

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



HX

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 209/30, 209/42, 405/14 C07D 409/14, 401/14, 471/04 A61K 31/40, 31/44	A1	(11) International Publication Number: WO 94/03427 (43) International Publication Date: 17 February 1994 (17.02.94)
(21) International Application Number: PCT/US93/07272 (22) International Filing Date: 2 August 1993 (02.08.93) (30) Priority data: 926,015 6 August 1992 (06.08.92) US (71) Applicant: WARNER-LAMBERT COMPANY [US/US]; 2800 Plymouth Road, Ann Arbor, MI 48105 (US). (72) Inventors: DOBRUSIN, Ellen, Myra ; 2205 Winchell Drive, Ann Arbor, MI 48104 (US). SHOWALTER, Howard, Daniel, Hollis ; 3578 Lamplighter Drive, Ann Arbor, MI 48103 (US). DENNY, William, Alexander ; 165 Gossamer Drive, Pakuranga, Auckland 2000 (NZ). PALMER, Brian, Desmond ; 1/27 Butterworth Drive, Glendene, Auckland 2000 (NZ). REWCASTLE, Gordon, William ; 107 Grande Vue Road, Manurewa, Auckland 2000 (NZ). TERCEL, Moana ; 67 Becroft Drive, Forrest Hill, Auckland 2000 (NZ). THOMPSON, Andrew, Mark ; 2/13 Raihiri Road, Mount Eden, Auckland 2000 (NZ).		(74) Agents: ATKINS, Michael, J.; Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Michigan 48105 (US) et al. (81) Designated States: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, RU, SK, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: 2-THIOINDOLES (SELENOINDOLES) AND RELATED DISULFIDES (SELENIDES) WHICH INHIBIT PROTEIN TYROSINE KINASES AND WHICH HAVE ANTITUMOR PROPERTIES (57) Abstract 2-Thioindoles (2-selenoindoles) and analogous 2-indolinethione (2-indolineselenone) and polysulfide (selenide) compounds, salts thereof, methods of production, intermediates in their production, pharmaceutical compositions containing said compounds, and methods for inhibiting protein kinase dependent disease in a mammal or treating aberrant cell growth in a mammal, using said compositions, are disclosed.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TC	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

-1-

2-THIOINDOLES (SELENOINDOLES) AND RELATED DISULFIDES
(SELENIDES) WHICH INHIBIT PROTEIN TYROSINE KINASES
AND WHICH HAVE ANTITUMOR PROPERTIES

5

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of
co-pending application U.S. Serial Number 926,015,
10 filed August 6, 1992.

FIELD OF INVENTION

15

The present invention relates to substituted
2-thioindoles (selenoindoles) and other related
compounds, which we have unexpectedly found to be
potent inhibitors of the epidermal growth factor
receptor tyrosine kinase (EGF-TK) and other protein
20 tyrosine kinases, and which show antitumor activity.
The invention also relates to use of the compounds as
inhibitors of protein tyrosine kinases and as antitumor
agents.

25

BACKGROUND OF THE INVENTION

30

Protein phosphorylation is a critical mechanism
for regulating protein function in the signal
transduction pathway in normal and transformed cells.
Protein tyrosine kinases (PTK) are an important class
of phosphorylating enzymes which mediate this
signalling and thereby regulate cell growth and
proliferation. PTKs catalyze the transfer of the
35 terminal phosphate from ATP to the phenol of tyrosine
in substrate proteins. Some growth factor receptors,

-2-

protooncogenes and oncogene products possess PTK activity. The overexpression or inappropriate expression of normal or mutant kinases can result in the loss of growth control and the unregulated cell proliferation associated with malignancy. Small molecules which selectively inhibit these enzymes are, therefore, of therapeutic interest as mediators of cell growth and as antitumor agents.

In some growth factor dependent tumors, the growth factor signal transduction pathway employs the intrinsic tyrosine kinase activity of the growth factor receptor for autophosphorylation and the phosphorylation of specific cellular proteins involved in mitogenesis and cell proliferation. Specific inhibitors of PTKs have been identified previously. It has been previously demonstrated that by uncoupling the PTK from the signal transduction pathway, inhibitors of the growth factor receptor tyrosine kinases result therapeutically in antitumor activity. This antitumor activity has been demonstrated both in vitro and in vivo. Most known tyrosine kinase inhibitors are styrene-like small molecules in which the aromatic ring is hydroxylated, resembling tyrosine itself.

For example, the EGF-TK inhibitor erbstatin is reported to inhibit the growth of human epidermoid carcinoma A431 cells with an $IC_{50} = 3.6 \mu g/mL$ (J. Antibiot. 1986;39:170). Erbstatin also inhibits the growth of the human mammary carcinoma MCF-7 and some esophageal tumors in nude mice in a dose-dependent manner (Eur. J. Cancer 1990;26(6):722 and Japanese Patent 03,109,323). Another class of PTK inhibitor called the tyrphostins also potently inhibited the EGF-dependent growth of A431 cells in vitro (J. Med. Chem. 1989;32:2344; J. Med. Chem. 1991;34:1896). The antitumor activity of two tyrphostins has been verified in vivo in nude mice bearing human squamous cell

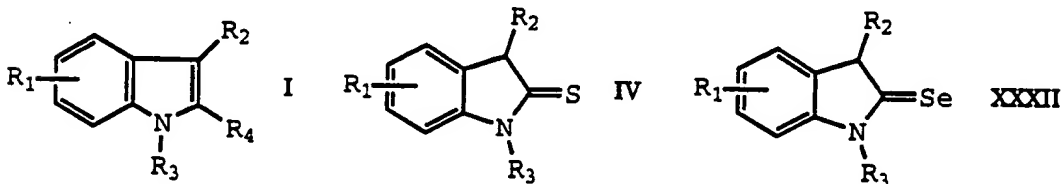
-3-

carcinoma MH-85 (Cancer Res. 1991;51:4430). In vitro and in vivo antitumor activity against A431 tumors has also been reported for a series of sulfonylbenzoyl nitrostyrenes (J. Med. Chem. 1991;34:2328) as TK inhibitors (J. Med. Chem. 1991;34:2328 and Helv. Chim. Acta 1992;75:696).

SUMMARY AND DETAILED DESCRIPTION

In one aspect, the invention relates to 2-thioindole (selenoindoles) and other related compounds that are potent inhibitors of epidermal growth factor receptor tyrosine kinase and other protein tyrosine kinases, and which have antitumor activity. Thus, the compounds are useful in dosage form as inhibitors of protein tyrosine kinases and as antitumor agents.

More particularly, the invention comprises 2-thioindole, 2-indolinethione, polysulfide, 2-selenoindole, 2-indolineselenone, and selenide compounds represented by the general Formulas I, IV, and XXXII



and pharmaceutically acceptable salts thereof, wherein

R₁ is a member selected from H, halogen, R, OH, OCOR, OR, CF₃, NO₂, NH₂, NHR, COOH, CONHR, (CH₂)_nOH, (CH₂)_nOR, (CH₂)_nNH₂, (CH₂)_nNHR, and (CH₂)_nNRR, and further represents replacement in the ring of 1 or 2 ring methine (-CH=) atoms with aza(-N=) atoms;

-4-

R_2 is a member selected from

C_{2-4} alkyl,

$(CH_2)_nCOOH$,

$(CH_2)_nCOOR$,

5 $(CH_2)_nCOR$,

$(CH_2)_nSO_2R$,

$(CH_2)_nSO_2NRR$,

$(CH_2)_nSO_2NHR$,

$CH=CHCOOH$,

10 $(CH_2)_nCH-COOH$,

|
OH

$(CH_2)_nCH-COOH$,

15 $(CH_2)_nCH-COOH$,

|
NH₂

$(CH_2)_nCONH_2$,

$(CH_2)_nCONHR$,

$(CH_2)_nCONRR$,

$(CH_2)_nCONHCH_2Ph$,

20 $CONHR$,

$CONRR$,

$CONHPh$,

COY ,

$COPhCOOH$,

25 $COPhCOOR$,

$(CH_2)_nCONHPh$,

$(CH_2)_nCONHPhR$,

SO_2Y ;

n is an integer from 1 to 4;

30 R is lower alkyl, preferably C_{1-4} alkyl;

R_3 is a member selected from H, lower alkyl, and benzyl;

Y represents a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring optionally

35 substituted with a lower alkyl, $COOH$, OH , $OCOR$, NH_2 , $CONHR$, $CONRR$, OR , or NHR group; and

R_4 represents SH , S_oX , S_oQ , SeH , Se_oX , and Se_oQ , where o is 1, 2, or 3, X is a member selected from H,

-5-

lower alkyl, benzyl, and benzene, pyridine, thiophene, furan, thiazole, and imidazole rings, and Q is another 2-thioindolyl or 2-selenoindolyl moiety of Formula I provided that the group does not comprise compounds having the names

2-(2-thioxo-3-indoliny)acetic acid,
2-(1-methyl-2-thioxo-3-indoliny)acetic acid,
methyl 2-(2-thioxo-3-indoliny)acetate,
ethyl 2-(1-methyl-2-thioxo-3-indoliny)acetate,
bis[methylindoliny-3-acetate-(2)]disulfide,
bis[indolyl-3-acetic acid-(2)]disulfide,
bis[methylindolyl-3-acetate-(2)]trisulfide, and
bis[1-methylindolyl-3-acetic acid-(2)]disulfide.

In another aspect, the invention relates to indolinethione compounds of the above Formula IV which exist as tautomers of compounds of Formula I wherein R_4 represents SH or indolineselenone compounds of the above Formula XXXII which exist as tautomers of compounds of Formula I wherein R_4 represents SeH. The invention comprises the thione or selenone compounds in their racemic and optical isomer forms. The thione or selenone compounds produced in the (\pm) form can be resolved as their (+) and (-) enantiomorphous optical isomers by per se art-recognized conventional means such as fractional crystallization of salts formed from optically active acids, separation of the isomers by chiral chromatography, or the chiral catalytic reduction of precursors.

In another aspect, the invention relates to pharmaceutical compositions useful for inhibition of protein tyrosine kinases and for antitumor activity containing as an active agent in a pharmaceutically acceptable carrier a therapeutically effective amount of a compound selected from 2-thioindole, 2-indolinethione, polysulfide, 2-selenoindole,

- 6 -

2-indolineselenone or selenide compounds represented by the above Formulas I, IV, and XXXII and pharmaceutically acceptable salts thereof, wherein

5 R_1 is a member selected from H, halogen, R, OH, OCOR, OR, CF_3 , NO_2 , NH_2 , NHR, COOH, CONHR, $(CH_2)_nOH$, $(CH_2)_nOR$, $(CH_2)_nNH_2$, $(CH_2)_nNHR$, and $(CH_2)_nNRR$, and further represents replacement in the ring of 1 or 2 ring methine ($-CH=$) atoms with aza ($-N=$) atoms;

10 R_2 is a member selected from
 lower alkyl, preferably C_{1-4} alkyl,
 $(CH_2)_nCOOH$,
 $(CH_2)_nCOOR$,
 $(CH_2)_nCOR$,
 $(CH_2)_nSO_2R$,
 15 $(CH_2)_nSO_2NRR$,
 $(CH_2)_nSO_2NHR$,
 $CH=CHCOOH$,
 $(CH_2)_nCH-COOH$,
 20 $\quad \quad \quad |$
 $\quad \quad \quad OH$
 $(CH_2)_nCH-COOH$,
 $\quad \quad \quad |$
 $\quad \quad \quad NH_2$
 $(CH_2)_nCONH_2$,
 25 $(CH_2)_nCONHR$,
 $(CH_2)_nCONRR$,
 $(CH_2)_nCONHCH_2Ph$,
CONHR,
CONRR,
 30 CONHPh,
COY,
COPhCOOH,
COPhCOOR,
 $(CH_2)_nCONHPh$,
 35 $(CH_2)_nCONHPhR$,
 SO_2Y ;

n is an integer from 1 to 4;

R is lower alkyl, preferably C_{1-4} alkyl;

-7-

R_3 is a member selected from H, lower alkyl and benzyl;

Y represents a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring optionally substituted with a lower alkyl, COOH, OH, OCOR, NH_2 , CONHR, CONRR, OR, or NHR group; and

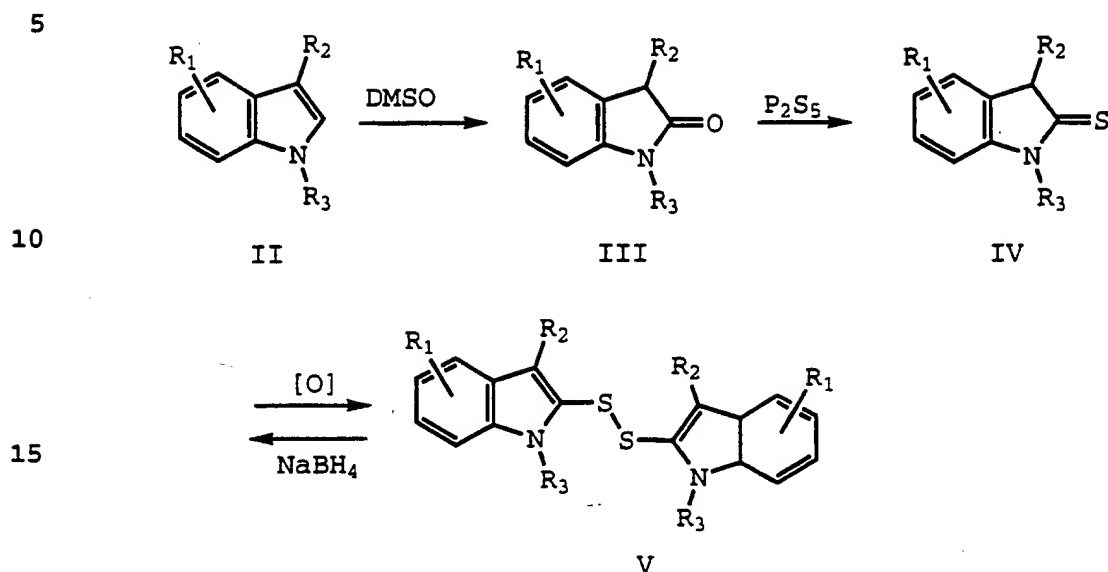
R_4 represents SH, S_oX , S_oQ , SeH, Se_oX , and Se_oQ , where o is 1, 2, or 3, X is a member selected from H, lower alkyl, benzyl, and benzene, pyridine, thiophene, furan, thiazole, and imidazole rings, and Q is another 2-thioindolyl or 2-selenoindolyl moiety of Formula I.

The invention comprises salt compounds formed by the basic or acidic thioindole compounds of the invention which form pharmaceutically acceptable salts with both organic and inorganic acids and/or organic and inorganic bases. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic, isethionic, and the like. Examples of suitable bases for salt formation are sodium and potassium carbonate, sodium and potassium hydroxide, ammonia, triethylamine, triethanolamine, and the like.

The compounds of Formulas I, IV, and XXXII can be prepared by the processes described in the following Reaction Schemes 1-11.

- 8 -

SCHEME 1



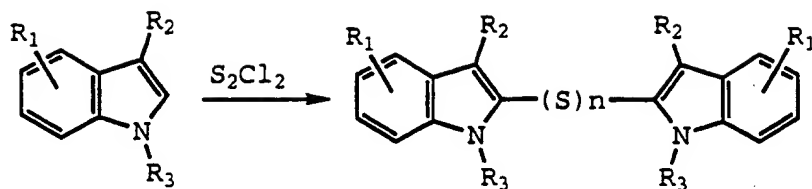
In Scheme 1, R_1 - R_3 are as designated for Formula I. Oxidation of 3-substituted indoles II in DMSO/HCl gives good yields of 3-substituted indolin-2-ones III which are thiated (preferably with P_2S_5 and $NaHCO_3$ or Na_2CO_3) to yield 3-substituted 2-indolinethiones IV. These compounds can be converted to the corresponding disulfides V by treatment with mild oxidizing agents (e.g., $FeCl_3$), and also undergo spontaneous oxidation to V in solution in air.

-9-

SCHEME 2

5

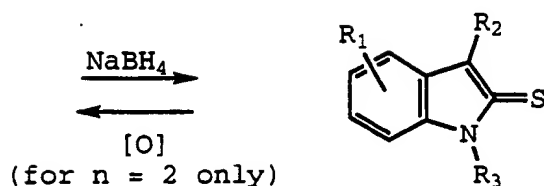
10



II

VI

15



IV

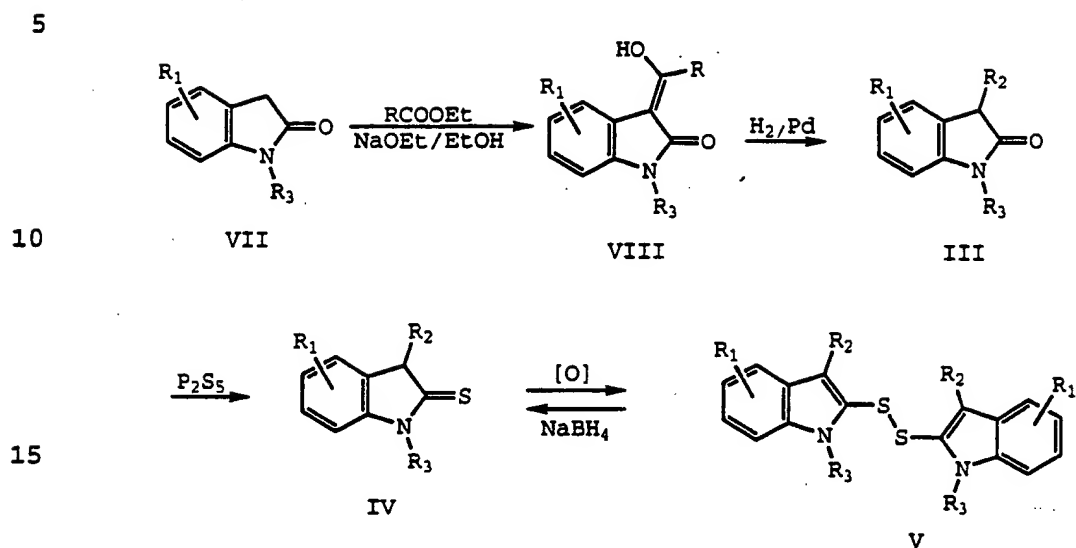
20

In Scheme 2, R₁-R₃ are as designated for Formula I. Treatment of 3-substituted indoles II with S₂Cl₂ gives mixtures of dimeric sulfides VI, where n = 1-3. These can be separated by chromatography, or more conveniently reduced to 2-indolinethiones IV with a mild reducing agent (preferably NaBH₄).

25

-10-

SCHEME 3

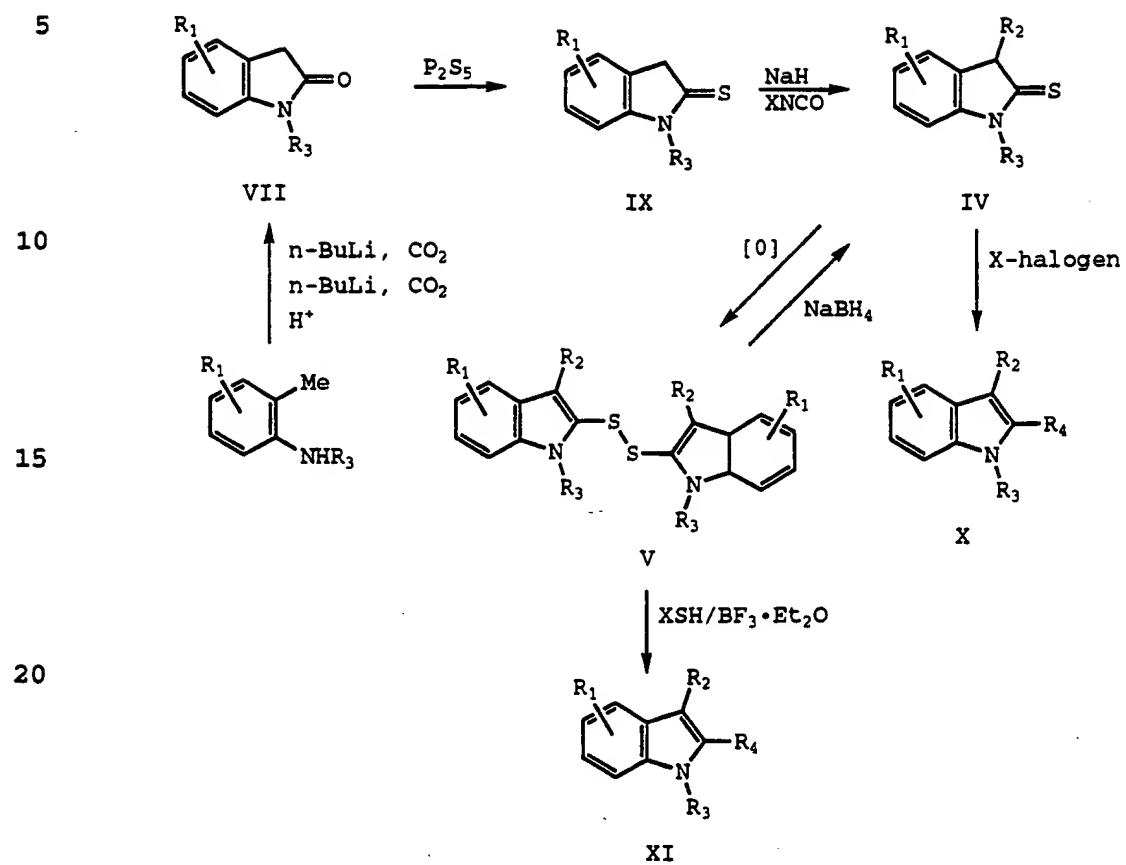


In Scheme 3, R_1 - R_3 are as designated for Formula I, and R represents $(CH_2)_nCOOH$, $(CH_2)_nCOOX$, $(CH_2)_nCONHX$, $(CH_2)_nSO_2X$, or $(CH_2)_nSO_2NX$, where n is from 0 to 4, and X is as designated for Formula I.

Treatment of 2-indolinones VII with diesters gives moderate yields of the isatylidene compounds VIII, which can be hydrogenated under acidic conditions to the 3-substituted indolin-2-ones III. Treatment of these as in Scheme 1 gives the desired compounds.

- 11 -

SCHEME 4

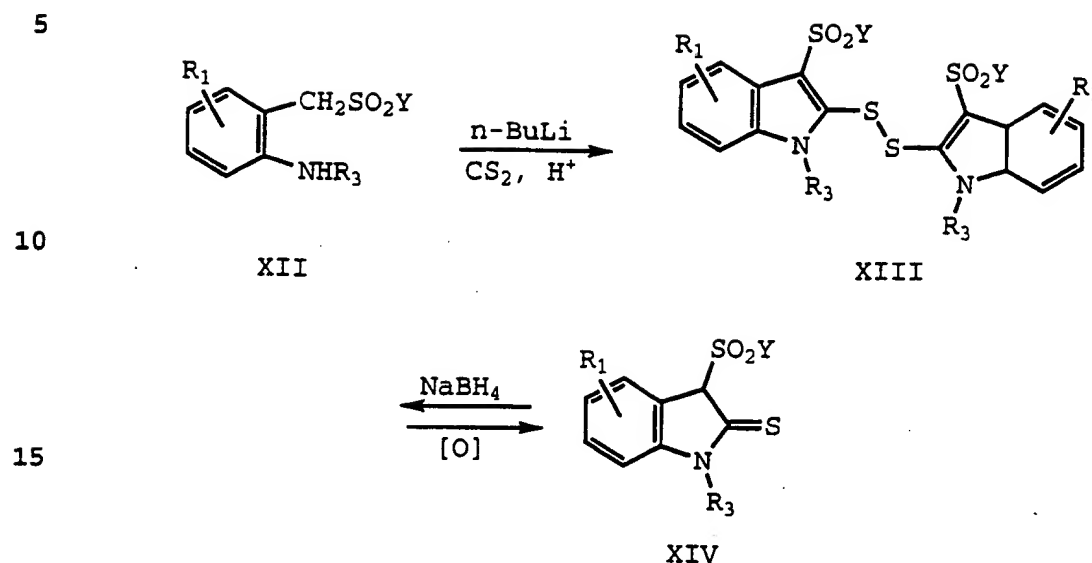


-12-

In Scheme 4, R_1 - R_4 , R and X are as designated for Formula I (except that X is not H). The ring-substituted oxindoles can be prepared by lithiation of the appropriately substituted ortho-toluidine derivatives, using CO_2 as both the N-protecting group and electrophile (Katritzky, Fan, Akutagawa, Wang, Heterocycles 1990;30:407). 2-Indolinones VII are thiated (preferably with P_2S_5 and $NaHCO_3$ or Na_2CO_3) to yield 2-indolinethiones IX. These compounds are deprotonated (typically with NaH in THF), and treated with an isocyanate to give 3-substituted 2-indolinethiones IV (where $R_2 = CONHX$). These compounds can be converted to the corresponding disulfides V as described in Scheme 1. The 3-substituted 2-indolinethiones IV can also react with alkylating agents (typically alkyl halides R-halogen) to give (X: where $R_4 = X$). Reaction of V with XSH gives mixed disulfides (XI: where $R_4 = SSX$).

-13-

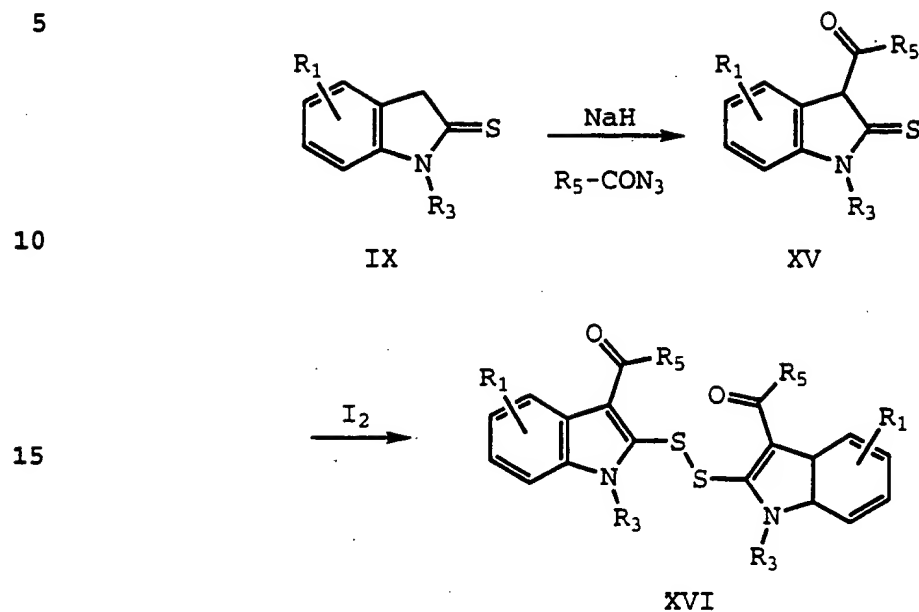
SCHEME 5



In Scheme 5, R_1 and R_3 are as designated for Formula I and Y represents lower alkyl or a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring, optionally substituted with a lower alkyl, COOH , OH , NH_2 , CONHR , OR , O , or NHR group. 2-Sulfonylmethyl anilines XII are treated sequentially with n-butyllithium and CS_2 , to give the disulfides XIII, which can be reduced to 2-indolinethiones XIV with a mild reducing agent (preferably NaBH_4).

-14-

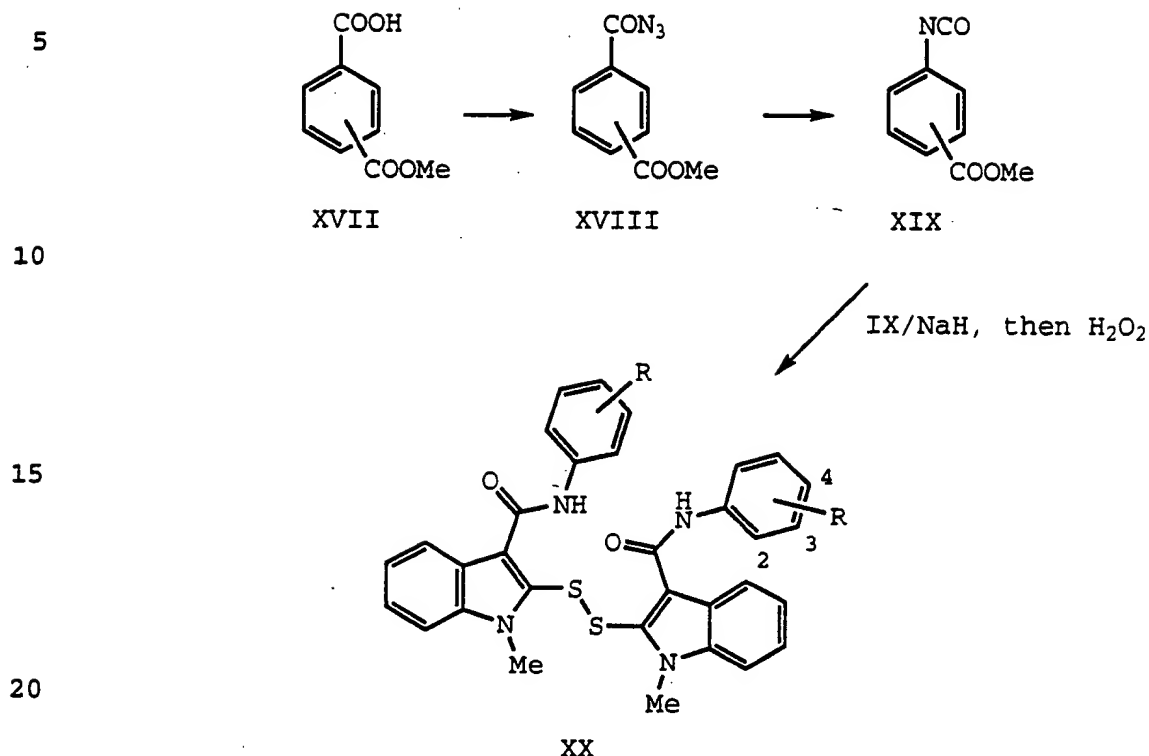
SCHEME 6



In Scheme 6, R_1 and R_3 are as designated for Formula I. Deprotonation of substituted 2-indolinethiones IX (typically with NaH in THF), followed by treatment with an acyl azide, gives 3-acyl-substituted 2-indolinethiones XV, where R_5 represents H, lower alkyl, benzyl, or a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring optionally substituted with a COOH, OH, NH_2 , CONHR, OR, NHR, or NRR group. Compounds XV can be converted into the disulfides XVI on mild oxidation (typically by treatment with I_2 or H_2O_2).

-15-

SCHEME 7



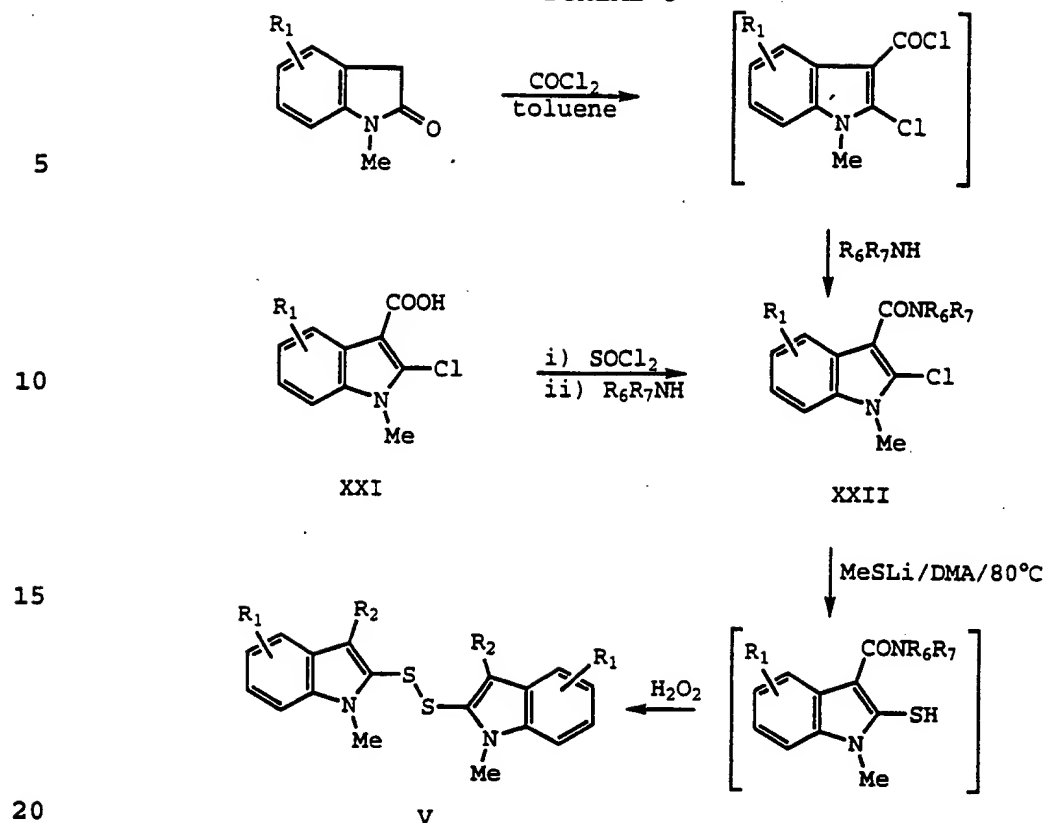
25 In Scheme 7, R is as designated for Formula I. Substituted aromatic and heteroaromatic acids (e.g., XVII) are converted to the corresponding acid chlorides (preferably with SOCl₂), and then to the corresponding acyl azides (e.g., XVIII) with NaN₃. Rearrangement to give the isocyanates (e.g., XIX) is carried out in an inert solvent (preferably toluene or xylene). These isocyanates (e.g., XIX) are converted to the disulfides (XX) by reaction with the sodium salt of 1-methyl-2-indolinethiones as outlined in Scheme 4. In suitable cases, hydrolysis of esters (XX; R = COOMe) with a mild base (preferably K₂CO₃) gives the corresponding acids (XX; R = COOH).

30

35

-16-

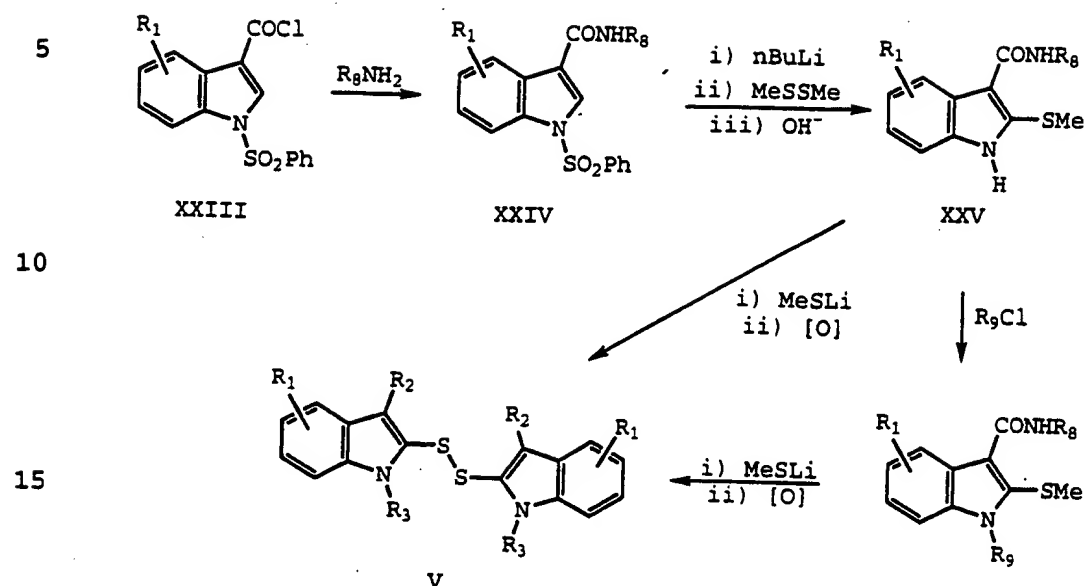
SCHEME 8



In Scheme 8, R_1 and R_2 are as designated for Formula I, and R_6 and R_7 are individually H, lower alkyl, benzyl, or a benzene ring optionally substituted with up to two of the groups COOH, OH, NH_2 , CONHR, OR, NHR, or NRR. 2-Chloro-1-methylindole-3-carboxyl chloride, prepared either from indolin-2-one and $COCl_2$ or from 2-chloro-1-methylindole-3-carboxylic acid (XXI) and $SOCl_2$, is reacted with amines HNR_6R_7 , or their salts, in an inert solvent (preferably 1,2-dichloroethane or CH_2Cl_2) and a base, if necessary, to give the amides (XXII). These compounds are heated with MeSLi in polar aprotic solvents (preferably dimethylacetamide) in an inert atmosphere to give intermediate thiol carboxamides, which are oxidized, (preferably with H_2O_2) to give the desired disulfides (V).

-17-

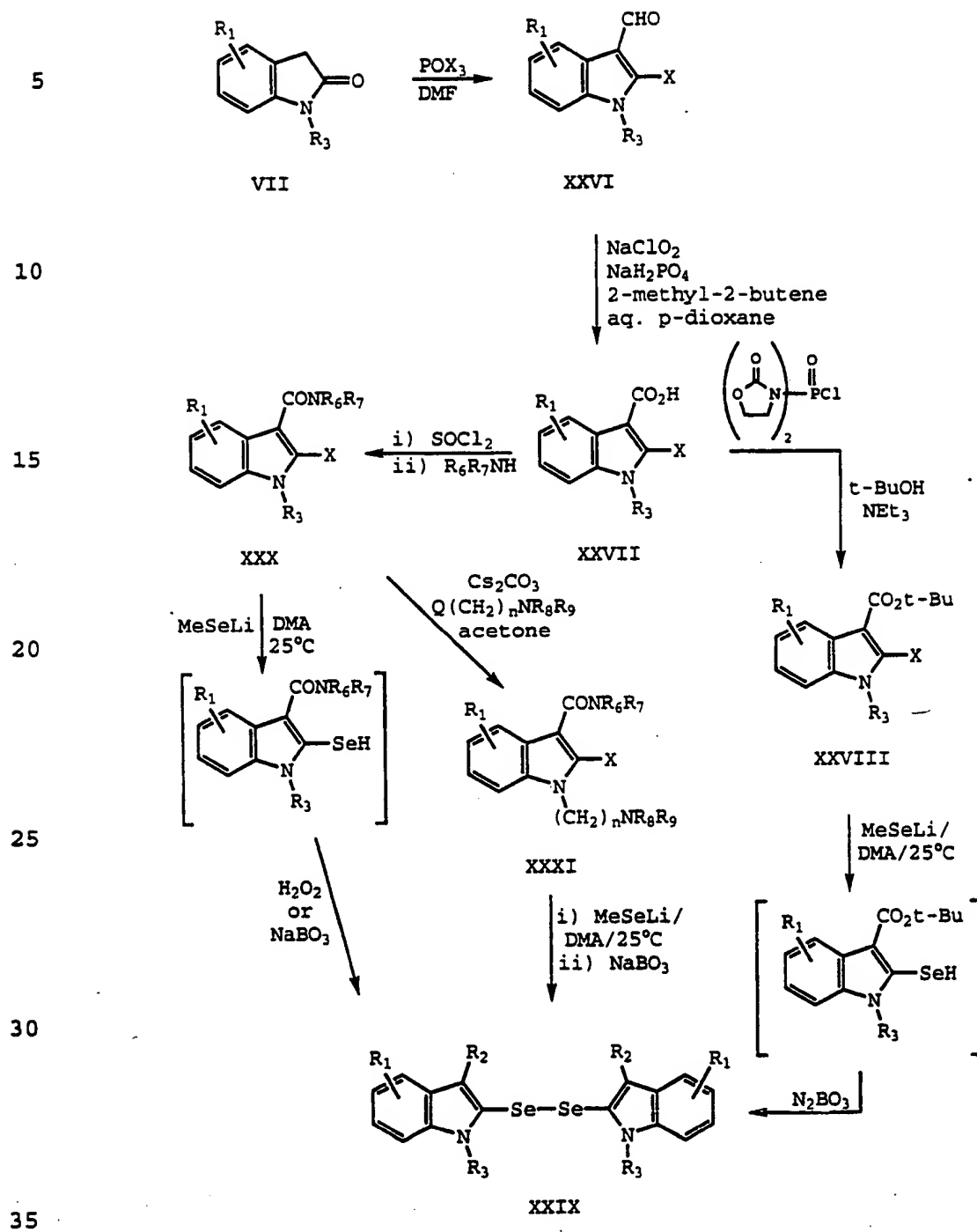
SCHEME 9



In Scheme 9, R₁, R₂, R₃, and R are as designated for Formula I. Reaction of acid chloride (XXIII) with amines gives amides (XXIV), where R₈ represents H, lower alkyl, benzyl, or a benzene ring optionally substituted with up to two of the groups COOH, OH, NH₂, CONHR, OR, NHR, or NRR. Compounds (XXIV) can be converted to 2-thioindoles (XXV) by lithiation and quenching with methyl sulfide, followed by base hydrolysis (preferably with K₂CO₃). The 2-thioindoles (XXV) can be converted to the desired disulfides (V) by dealkylation (preferably with lithium thiomethoxide) and mild oxidation (preferably with I₂ or H₂O₂). Compounds (XXV) can also be alkylated with an alkyl halide (e.g., R₉Cl), where R₉ represents lower alkyl, benzyl, or benzyl optionally substituted with up to two of the groups COOH, OH, NH₂, CONHR, OR, NHR, or NRR, and a base (preferably K₂CO₃).

- 18 -

SCHEME 10



-19-

In Scheme 10, R_1 is as designated for Formula I and R_6 and R_7 are individually H , lower alkyl, benzyl, or a benzene ring optionally substituted with up to two of the groups $COOH$, OH , NH_2 , $CONHR$, OR , NHR , or NRR .

5 R_3 is H or lower alkyl, and X = any halogen, preferably bromine or chlorine. Substituted 2-halo-3-indole carboxylic acids XXVII, prepared by oxidation of corresponding substituted 3-carboxaldehydes, are reacted with amines HNR_6R_7 or their salts in an inert

10 solvent (preferably 1,2-dichloroethane or CH_2Cl_2) and a base, if necessary, to give the amides XXX. These compounds are reacted with $MeSeLi$ in polar aprotic solvents (preferably dimethylacetamide) to give intermediate selenol carboxamides, which are oxidized

15 with H_2O_2 or $NaBO_4$ to give the desired diselenides XXIX. Alternatively, intermediate XXX, where $R_3 = H$, can be reacted with a haloalkyl amine, or its salt, where $Q = Cl, Br, I$ (preferably Cl) and R_8, R_9 are as defined in Formula I, but preferably R_8 and R_9 are H ,

20 alkyl, cycloalkyl, and $n = 1-4$ in a polar solvent (preferably acetone) and anhydrous metal carbonate (preferably cesium carbonate) to give intermediate XXXI which is converted to diselenide XXIX as described above for intermediate XXX. Additionally, intermediate

25 acid XXVII can be converted to the substituted 2-halo-3-indole carboxylic acid tertiary butyl ester XXVIII, which can be further reacted with $MeSeLi$ as described above for intermediate XXX to give the target substituted diselenide XXIX where $R_2 = COO$ -tertiarybutyl.

-20-

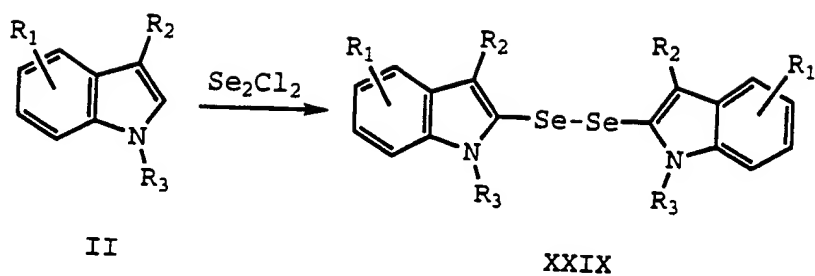
SCHEME 11

5

10

15

20



In Scheme 11, R₁-R₃ are as designated for Formula I. Treatment of 3-substituted indoles II with Se₂Cl₂ gives the diselenide XXIX.

-21-

As indicated, the compounds of this invention that are basic can form acidic salts and those that are acidic can form basic salts. All such salts are within the scope of this invention and they can be prepared by conventional methods. For example, they can be prepared simply by contacting the acidic and basic entities, usually in a stoichiometric ratio, in either an aqueous, nonaqueous or partially aqueous medium, as appropriate. The salts are recovered either by filtration, by precipitation followed by filtration, by evaporation of the solvent, or in the case of aqueous solutions, by lyophilization, as appropriate.

The compounds of this invention are readily adapted to therapeutic use for the control of tyrosine kinase dependent diseases in mammals. Tyrosine kinase dependent diseases comprise hyperproliferative disorders which are initiated and/or maintained by aberrant tyrosine kinase enzyme activity. Tyrosine kinase inhibitors can therefore have beneficial therapeutic effects against aberrant cell growth disorders such as various cancers, atherosclerosis, angiogenesis (tumor growth/metastasis, diabetic retinopathy, for example), viral diseases (HIV infections, for example), and the like.

Tyrosine kinase dependent diseases further comprise cardiovascular diseases which are related to aberrant tyrosine kinase enzyme activity. Tyrosine kinase inhibitors can therefore have beneficial therapeutic effects against such cardiovascular diseases as restenosis. It should be understood that restenosis is an example of a cardiovascular disease which is dependent upon tyrosine kinase; one skilled in the art, however, will be aware of other examples of cardiovascular diseases which are dependent upon tyrosine kinase.

-22-

The compounds are administered either orally or parenterally, or topically as eye drops, in dosages ranging from about 0.1 to 10 mg/kg of body weight per day in single or divided doses. Of course, in particular situations, at the discretion of the attending physician, doses outside of this range will be used.

The compounds of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, elixirs, syrups, injectable or eye drop solution, and the like. Such carriers include solid diluents or fillers, sterile aqueous media, and various nontoxic organic solvents.

For purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate, and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch, alginic acid, and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin, and acacia. Additionally, lubrication agents such as magnesium stearate, sodium lauryl sulfate, and talc are often very useful for tableting purposes. Solid compositions of similar type are also employed as fillers in soft- and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents, and/or suspending agents as well as such diluents as water, ethanol,

-23-

propylene glycol, glycerin, and various like combinations thereof.

For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water soluble, alkali metal, or alkaline earth metal salts previously enumerated. Such aqueous solution should be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well known to those skilled in the art.

For purposes of topical administration, dilute sterile, aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared in containers suitable for dropwise administration to the eye.

In a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, the weight ratio of carrier to active ingredient will normally be in the range from 1:4 to 4:1, and preferably 1:2 to 2:1. However, in any given case, the ratio chosen will depend on such factors as the solubility of the active component, the dosage contemplated and the precise route of administration.

The following Table 1 sets out physical data for 137 compounds within the general Formula I, representative of it, and preparable by the processes of the invention.

35

TABLE 1

No.	Formula	Chemical Structure				mp (°C)	Molecular Formula	Analysis ^a
		A	B	B1				
5								
10								
15								
20								
1	A	H	H	H	H	166-168	C ₁₀ H ₉ NO ₂ S	known ^d
2	A	H	Me	Me	H	150-153	C ₁₁ H ₁₁ NO ₂ S	known ^d
3	A	H	H	H	H	150-152	C ₁₁ H ₁₁ NO ₂ S	C, H, N, S ^e
4	A	H	Me	Me	H	68-70	C ₁₂ H ₁₃ NO ₂ S	C, H, N, S
5	A	H	Me	Me	H	47-48	C ₁₃ H ₁₅ NO ₂ S	C, H, N, S ^e
6	A	H	H	H	H	193-195	C ₁₇ H ₁₀ N ₂ OS	C, H, N, S
7	A	H	H	H	H	170-173	C ₁₁ H ₁₁ NO ₂ S	C, H, N
8	A	H	Me	Me	H	126-128.5	C ₁₂ H ₁₃ NO ₂ S · 0.25H ₂ O	C, H, N, S
9	A	H	H	H	H	95.5-98	C ₁₂ H ₁₃ NO ₂ S	C, H, N, S

TABLE 1 (cont'd)

No.	Formula	R ₁	R ₂	R ₃	X	mp (°C)	Molecular Formula	Analysis ^a
5	10	A	H	H	H	oil ^b	C ₁₃ H ₁₃ NO ₂ S	C, H, N, S
	11	A	H	Me	H	71-73	C ₁₃ H ₁₅ NO ₂ S	C, H, N, S
	12	A	H	Me	H	61-63	C ₁₄ H ₁₇ NO ₂ S	C, H, N, S
	13	A	H	H	H	149.5-151	C ₁₈ H ₁₈ NO ₂ S · 0.5H ₂ O	C, H, N, S
	14	A	H	H	H	160-163	C ₁₁ H ₁₂ N ₂ OS	C, H, N, S
10	15	A	H	H	H	132-134	C ₁₂ H ₁₃ NO ₂ S	C, H, N, S
	16	A	H	Me	H	144-146.5	C ₁₃ H ₁₅ NO ₂ S · H ₂ O	C, H, N, S
	17	A	H	H	H	109-110	C ₁₃ H ₁₅ NO ₂ S	C, H, N, S
	18	A	H	Me	H	103-106	C ₁₄ H ₁₇ NO ₂ S	C, H, N, S
	19	A	7-aza CONHPh	Me	H	162-164	C ₁₅ H ₁₃ N ₃ O ₂ S · CH ₃ OH	C, H, N, S
	20	A	5-Cl CONHPh	Me	H	312-320	C ₁₆ H ₁₃ ClN ₂ OS	HRMS
15	21	A	H	Me	H	149-151	C ₁₆ H ₁₄ N ₂ OS	C, H, N, S
	22	A	H	Me	Me	116-118	C ₁₇ H ₁₆ N ₂ OS	C, H, N, S
	23	A	H	Me	CH ₂ Ph	144-146	C ₂₃ H ₂₀ N ₂ OS ₂	C, H, N, S
	24	A	H	Me	H	130-132	C ₁₆ H ₁₃ NOS	C, H, N, S
	25	A	H	Me	H	282 (dec)	C ₁₇ H ₁₃ NO ₃ S · 0.25H ₂ O	C, H, N
	26	A	H	Me	H	164-166	C ₁₈ H ₁₅ NO ₃ S	C, H, N, S
20	27	B	H	H	-	160-162	C ₂₂ H ₂₀ N ₂ O ₄ S ₂	C, H, N, S ^f
	28	B	H	Me	-	130-132.5	C ₂₄ H ₂₄ N ₂ O ₄ S ₂	C, H, N, S
	29	B	H	H	-	196-199	C ₂₀ H ₁₆ N ₂ O ₄ S ₂	known ^d
	30	B	H	H	S	199-202	C ₂₀ H ₁₆ N ₂ O ₄ S ₃	C, H, N, S
	31	B	H	H	S	130-132	C ₂₂ H ₂₀ N ₂ O ₄ S ₃	C, H, N, S ^f
	32	B	H	Me	-	190-192.5	C ₂₂ H ₂₀ N ₂ O ₄ S ₂	known ^d

TABLE 1 (cont'd)

No.	Formula	R ₁	R ₂	R ₃	X	mp (°C)	Molecular Formula	Analysis ^a
33	B	H	CH ₂ COOEt	Me	-	117-119	C ₂₆ H ₂₈ N ₂ O ₄ S ₂	C, H, N, S
34	B	H	CH ₂ CONHCH ₂ Ph	H	-	200.5-203.5	C ₃₄ H ₃₀ N ₄ O ₂ S ₂	C, H, N, S
35	B	H	CH ₂ CN	H	-	168.5-169.5	C ₂₀ H ₁₄ N ₄ S ₂ (lit ref) ⁸	C, H, N, S
36	B	H	(CH ₂) ₂ COOH	H	-	118-120.5	C ₂₂ H ₂₀ N ₂ O ₄ S ₂ ·H ₂ O	C, H, N, S
37	B	H	(CH ₂) ₂ COOH	Me	-	158.5-160	C ₂₄ H ₂₄ N ₂ O ₄ S ₂	C, H, N, S
38	B	H	(CH ₂) ₂ COOEt	H	-	137-139	C ₂₆ H ₂₈ N ₂ O ₄ S ₂	C, H, N, S
39	B	H	(CH ₂) ₂ COOMe	H	-	162.5-164	C ₂₄ H ₂₄ N ₂ O ₄ S ₂	C, H, N, S
40	B	H	(CH ₂) ₂ COOMe	Me	-	139-141.5	C ₂₆ H ₂₈ N ₂ O ₄ S ₂	C, H, N, S
41	B	5-Me	(CH ₂) ₂ COOH	H	-	91.5-95	C ₂₄ H ₂₄ N ₂ O ₄ S ₂	HRMS ^c
42	B	5-Me	(CH ₂) ₂ COOEt	H	-	138.5-139	C ₂₈ H ₃₂ N ₂ O ₄ S ₂ ·0.5C ₆ H ₆	C, H, N, S
43	B	6-Me	(CH ₂) ₂ COOH	H	-	126-128	C ₂₄ H ₂₄ N ₂ O ₄ S ₂ ·0.5H ₂ O	C, H, N, S
44	B	6-Me	(CH ₂) ₂ COOEt	H	-	122-123.5	C ₂₈ H ₃₂ N ₂ O ₄ S ₂	C, H, N, S
45	B	7-Me	(CH ₂) ₂ COOH	H	-	172.5-175	C ₂₄ H ₂₄ N ₂ O ₄ S ₂	C, H, N
46	B	7-Me	(CH ₂) ₂ COOEt	H	-	120-122.5	C ₂₈ H ₃₂ N ₂ O ₄ S ₂	C, H, N, S
47	B	H	(CH ₂) ₂ CONHCH ₂ Ph	H	-	141-144	C ₃₆ H ₃₄ N ₄ O ₂ S ₂	C, H, N, S
48	B	H	(CH ₂) ₂ CN	H	-	167-169	C ₂₁ H ₁₆ N ₄ S ₂ (lit ref) ⁸	
49	B	H	(CH ₂) ₂ NO ₂	H	-	153-154	C ₂₀ H ₁₈ N ₄ O ₄ S ₂ ·0.5H ₂ O	C, H, N, S
50	B	H	(CH ₂) ₂ CONH ₂	H	-	101 (dec)	C ₂₂ H ₂₂ N ₄ O ₂ S ₂ ·0.5H ₂ O	C, H, N, S
51	B	H	(CH ₂) ₂ CONHMe	H	-	162.5-164	C ₂₄ H ₂₆ N ₄ O ₂ S ₂	C, H, N, S
52	B	H	(CH ₂) ₂ CONHOMe	H	-	176-178	C ₂₄ H ₂₆ N ₄ O ₄ S ₂	C, H, N, S
53	B	H	(CH ₂) ₂ CONMe ₂	H	-	179-180	C ₂₆ H ₃₀ N ₄ O ₂ S ₂	C, H, N, S
54	B	H	(CH ₂) ₂ CONH(CH ₂) ₂ Ph	H	-	oil	C ₃₈ H ₃₈ N ₄ O ₂ S ₂	HRFABMS
55	B	H	(CH ₂) ₂ CONHCH ₂ Ph{4-COOMe}	H	-	151-153	C ₄₀ H ₃₈ N ₄ O ₆ S ₂	C, H, N, S

5

10

15

20

25

TABLE 1 (cont'd)

No.	Formula	R ₁	R ₂	R ₃	X	mp (°C)	Molecular Formula	Analysis ^a
56	B	H	(CH ₂) ₂ CONHCH ₂ Ph {4-COOH}	H	-	135.5-138.5 (dec)	C ₃₈ H ₃₄ N ₄ O ₆ S ₂ ·H ₂ O	C, H, N, S
57	B	H	(CH ₂) ₂ CONHCH ₂ Ph {3-OH, 4-COOH}	H	-	183-185	C ₄₀ H ₃₈ N ₄ O ₆ S ₂	C, H, N, S
58	B	H	(CH ₂) ₂ CONHCH ₂ Ph {3-OH, 4-COOH}	H	-	160-163.5 (dec)	C ₃₈ H ₃₄ N ₄ O ₆ S ₂ ·H ₂ O	C, H, N, S
59	B	H	(CH ₂) ₂ CONHPh	H	-	114 (dec)	C ₃₄ H ₃₀ N ₄ O ₂ S ₂ ·0.5H ₂ O	C, H, N, S
60	B1	H	NHAc	H	-	140-144 [#] (dec)	C ₄₀ H ₄₀ N ₆ O ₄ S ₂ ·0.5H ₂ O	C, H, N, S
				-	-	154.5-157.5 [#] (dec)	C ₄₀ H ₄₀ N ₆ O ₄ S ₂	C, H, N, S
61	B1	H	NHCOCF ₃	H	-	160-164 (dec)	C ₄₀ H ₃₄ F ₆ N ₆ O ₄ S ₂ ·0.5H ₂ O	C, H, N, S
62	B1	H	NH ₂	H	-	147-150 (dec)	C ₃₆ H ₃₆ N ₆ O ₂ S ₂ ·0.5H ₂ O	C, H, N, S
63	B1	H	OAc	H	-	120-124 (dec)	C ₄₀ H ₃₄ N ₄ O ₆ S ₂	C, H, N, S
64	B1	H	OH	H	-	120-125	C ₃₆ H ₃₄ N ₄ O ₄ S ₂	C, H, N, S
65	B	H	(CH ₂) ₃ COOH	H	-	141-143.5	C ₂₄ H ₂₄ N ₂ O ₄ S ₂ ·0.5H ₂ O	C, H, N, S
66	B	H	(CH ₂) ₃ COOH	Me	-	106.5-109.5	C ₂₆ H ₂₈ N ₂ O ₄ S ₂ ·2AcOH	C, H, N, S
67	B	H	(CH ₂) ₃ COOMe	H	-	91-93	C ₂₆ H ₂₈ N ₂ O ₄ S ₂	C, H, N, S
68	B	H	(CH ₂) ₃ COOMe	Me	-	112-113	C ₂₈ H ₃₂ N ₂ O ₄ S ₂	C, H, N, S
69	B	H	(CH ₂) ₃ CONHCH ₂ Ph	H	-	98.5-101	C ₃₈ H ₃₈ N ₄ O ₂ S ₂	C, H, N, S
70	B	H	CONHPh	Me	-	187-188	C ₃₂ H ₂₆ N ₄ O ₂ S ₂	C, H, N, S
71	B	H	CONHPh	Et	-	200-202	C ₃₄ H ₃₀ N ₄ O ₂ S ₂	C, H, N, S
72	B	4-Cl	CONHPh	Me	-	225-228	C ₃₂ H ₂₄ Cl ₂ N ₄ O ₂ S ₂	C, H, N, Cl
73	B	5-Cl	CONHPh	Me	-	214-216	C ₃₂ H ₂₄ Cl ₂ N ₄ O ₂ S ₂	C, H, N, S
74	B	7-Cl	CONHPh	Me	-	232-234	C ₃₂ H ₂₄ Cl ₂ N ₄ O ₂ S ₂	C, H, N, Cl
75	B	4-Me	CONHPh	Me	-	237-239	C ₃₄ H ₃₀ N ₄ O ₂ S ₂	C, H, N, S
76	B	5-Me	CONHPh	Me	-	231-234	C ₃₄ H ₃₀ N ₄ O ₂ S ₂	C, H, N, S

TABLE 1 (cont'd)

No.	Formula	R ₁	R ₂	R ₃	X	mp (°C)	Molecular Formula	Analysis ^a
77	B	6-Me	CONHPh	Me	-	192-195	C ₃₄ H ₃₀ N ₄ O ₂ S ₂	C, H, N, S
78	B	7-Me	CONHPh	Me	-	221-223	C ₃₄ H ₃₀ N ₄ O ₂ S ₂	C, H, N, S
79	B	4-OMe	CONHPh	Me	-	225-228	C ₃₄ H ₃₀ N ₄ O ₂ S ₂	C, H, N, S
80	B	5-OMe	CONHPh	Me	-	161-164	C ₃₄ H ₃₀ N ₄ O ₂ S ₂	C, H, N, S
81	B	6-OMe	CONHPh	Me	-	197-200	C ₃₄ H ₃₀ N ₄ O ₂ S ₂	C, H, N, S
82	B	7-OMe	CONHPh	Me	-	205-206	C ₃₄ H ₃₀ N ₄ O ₂ S ₂	C, H, N, S
83	B	7-aza	CONHPh	Me	-	197-198	C ₃₀ H ₂₄ N ₆ O ₂ S ₂	C, H, N, S
84	B	5-CF ₃	CONHPh	Me	-	214-216	C ₃₄ H ₂₄ F ₆ N ₄ O ₂ S ₂	C, H, N, S
85	B	6-Cl	CONHPh	Me	-	243-245	C ₃₂ H ₂₄ Cl ₂ N ₄ O ₂ S ₂	C, H, N, S
86	B	5-NO ₂	CONHPh	Me	-	236-240	C ₃₂ H ₂₄ N ₆ O ₆ S ₂ · 2H ₂ O	C, H, N
87	B	5-F	CONHPh	Me	-	205-207	C ₃₂ H ₂₄ F ₂ N ₄ O ₂ S ₂	C, H, N, S
88	B	5-CN	CONHPh	Me	-	221-224	C ₃₄ H ₂₄ N ₆ O ₂ S ₂ · 0.5H ₂ O	C, H, N, S
89	B	5-Br	CONHPh	Me	-	219-221	C ₃₂ H ₂₄ Br ₂ N ₄ O ₂ S ₂	C, H, N, S
90	B	4-OAc	CONHPh	Me	-	194	C ₃₆ H ₃₀ N ₄ O ₆ S ₂	HRFABMS
91	B	5-OAc	CONHPh	Me	-	147-150	C ₃₆ H ₃₀ N ₄ O ₆ S ₂ · 0.5H ₂ O	C, H, N, S
92	B	5-OH	CONHPh	Me	-	185-187	C ₃₂ H ₂₆ N ₄ O ₄ S ₂ · H ₂ O	C, H, N
93	B	6-OAc	CONHPh	Me	-	219-222	C ₃₆ H ₃₀ N ₄ O ₆ S ₂	C, H, N, S
94	B	6-OH	CONHPh	Me	-	185-187	C ₃₂ H ₂₆ N ₄ O ₄ S ₂	HRMS
95	B	7-OAc	CONHPh	Me	-	212-214	C ₃₆ H ₃₀ N ₄ O ₆ S ₂ · 0.5H ₂ O	C, H, N, S
96	B	7-OH	CONHPh	Me	-	206-207	C ₃₂ H ₂₆ N ₄ O ₄ S ₂	C, H, N, S
97	B	H	CONHMe	Me	-	162-165	C ₂₂ H ₂₂ N ₄ O ₂ S ₂	HRMS ^c
98	B	H	CONHCH ₂ Ph	Me	-	145-147	C ₃₄ H ₃₀ N ₄ O ₂ S ₂	C, H, N, S
99	B	H	SO ₂ Ph ₂ -Me	H	-	230-233	C ₃₀ H ₂₄ N ₂ O ₄ S ₄	C, H, N, S
100	B	H	COPh	Me	-	199-202	C ₃₂ H ₂₄ N ₂ S ₂ O ₂	C, H, N, S

5

10

15

20

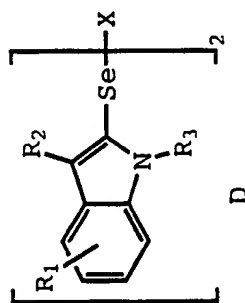
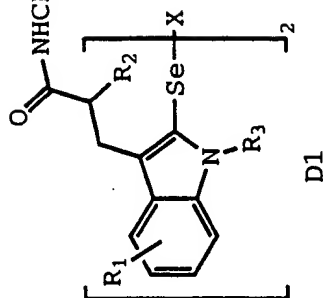
25

TABLE 1 (cont'd)

No.	Formula	R ₁	R ₂	R ₃	X	mp (°C)	Molecular Formula	Analysis ^a
5	101	B	H	COPhpCOOH	Me	241-246	C ₃₄ H ₂₄ N ₂ S ₂ O ₆ ·1.5H ₂ O	C, H
	102	B	H	COPhpCOOMe	Me	200-203	C ₃₆ H ₂₈ N ₂ O ₆ S ₂	C, H, N, S
	103	B	H	Me	Me	113-115	C ₂₀ H ₂₀ N ₂ S ₂	C, H, N, S
10	104	B	H	CONHPh{4-COOMe}	Me	184-186	C ₃₆ H ₃₀ N ₄ O ₆ S ₂ ·H ₂ O	C, H, N, S
	105	B	H	CONHPh{4-COOH}	Me	221	C ₃₄ H ₂₆ N ₄ O ₆ S ₂ ·0.5H ₂ O	C, H, N, S
	106	B	H	CONHPh{3-COOMe}	Me	193-195	C ₃₆ H ₃₀ N ₄ O ₆ S ₂	C, H, N, S
	107	B	H	CONHPh{3-COOH}	Me	219-220	C ₃₄ H ₂₆ N ₄ O ₆ S ₂	C, H, N, S
	108	B	H	CONHPh{2-COOMe}	Me	179-181	C ₃₆ H ₃₀ N ₄ O ₆ S ₂	C, H, N, S
	109	B	H	CONHPh{2-COOH}	Me	184-186	C ₃₄ H ₂₆ N ₄ O ₆ S ₂	C, H, N, S
	110	B	H	CONHCH ₂ Ph{4-COOMe}	Me	178-180	C ₃₈ H ₃₄ N ₄ O ₆ S ₂	C, H, N, S
15	111	B	H	CONHCH ₂ Ph{4-COOH}	Me	178-180	C ₃₆ H ₃₀ N ₄ O ₆ S ₂ ·1.5H ₂ O	C, H, N, S
	112	B	H	CONHCH ₂ COOH	Me	196-198	C ₂₄ H ₂₂ N ₄ O ₆ S ₂	C, H, N, S
	113	B	H	CON (Me) Ph	Me	158-163	C ₃₄ H ₃₁ N ₄ S ₂ O ₂	C, H, N, S
	114	B	H	CONHCH ₂ CH (OH) CH ₂ OH	Me	198	C ₂₆ H ₃₀ N ₄ O ₆ S ₂	C, H, N, S
	115	B	H	CONHCH ₂ CH ₂ NMe ₂	Me	163.5-165	C ₂₈ H ₃₆ N ₆ O ₂ S ₂	C, H, N, S
20	116	B	H	CONH-4-pyridyl	Me	226-229	C ₃₀ H ₂₄ N ₆ O ₂ S ₂	C, H, N, S
	117	B	H	CONH-3-pyridyl	Me	257-260	C ₃₀ H ₂₄ N ₆ O ₂ S ₂	C, H, N, S
	118	B	H	CONH ₂	Me	186-188	C ₂₀ H ₁₈ N ₄ O ₂ S ₂ ·0.5H ₂ O	C, H, N, S
	119	B	H	CONMe ₂	Me	96-102	C ₂₄ H ₂₆ N ₄ O ₂ S ₂ ·0.5H ₂ O	C, H, N
	120	B	H	CN	Me	205-207	C ₂₀ H ₁₄ N ₄ S ₂	C, H, N, S
25	121	B	H	COMe	Me	178.5-179.5	C ₂₂ H ₂₀ N ₂ O ₂ S ₂ ·0.5H ₂ O	C, H, N, S
	122	B	H	CONH-2-pyridyl	Me	270-272	C ₃₀ H ₂₄ N ₆ O ₂ S ₂ ·0.25H ₂ O	C, H, N, S
	123	B	H	CONH-furyl	Me	175-176	C ₂₈ H ₂₀ N ₂ O ₄ S ₂	C, H, N, S
	124	B	H	CONH-thienyl	Me	183 (DEC)	C ₂₈ H ₂₂ N ₄ O ₄ S ₂ ·0.5H ₂ O	C, H, N

TABLE 1 (cont'd)

N .	Formula	R ₁	R ₂	R ₃	X	mp (°C)	Molecular Formula	Analysis ^a
125	B	H	CONHCH ₂ Ph	H	-	203-205	C ₃₂ H ₂₆ N ₄ O ₂ S ₂	C, H, N, S
126	B	H	CONHPh	H	-	220-222.5	C ₃₀ H ₂₂ N ₄ O ₂ S ₂	C, H, N, S
5	127	B	CONHMe	H	-	232-236	C ₂₀ H ₁₈ N ₄ O ₂ S ₂	C, H, N, S
128	B	H	CONHPh	(CH ₂) ₃ NMe ₂	-	165	C ₂₈ H ₃₆ N ₆ O ₂ S ₂	C, H, N, S



129	D	H	COOt-Bu	CH ₃	-	187-189	C ₂₈ H ₃₂ N ₂ O ₄ Se ₂ · 0.2H ₂ O	C, H, N
130	D	H	COOH	CH ₃	-	174 (dec)	C ₂₀ H ₁₆ N ₂ O ₄ Se ₂ · 0.1H ₂ O	C, H, N
131	D	H	CONHMe	CH ₃	-	225-230 (dec)	C ₂₂ H ₂₂ N ₄ O ₂ Se ₂ · 0.9H ₂ O	C, H, N
132	D	H	CONH(CH ₂) ₂ NMe ₂	CH ₃	-	160-164	C ₃₂ H ₄₄ N ₆ O ₂ Se ₂ · 2.0HCl · 1.7H ₂ O	C, H, N, Cl

10

15

20

25

TABLE 1 (cont'd)

No.	Formula	R ₁	R ₂	R ₃	X	mp (°C)	Molecular Formula	Analysis ^a
133	D	H	CONHCH ₃	H	-	272-275	C ₂₀ H ₁₈ N ₄ O ₂ Se ₂ · 0.9H ₂ O	C, H, N
134	D	H	CONH(CH ₂) ₂ NEt ₂	H	-	257-259 (dec)	C ₃₀ H ₄₀ N ₆ O ₂ Se ₂ · 2.0HCl·H ₂ O	C, H, N
135	D	H	CONHCH ₃	(CH ₂) ₂ NEt ₂	-	156-157	C ₃₂ H ₄₄ N ₆ O ₂ Se ₂ ·0.5H ₂ O	C, H, N
136	D1	H	NH ₂ [R-(R*, R*)]	H	-	172-174	C ₃₆ H ₃₆ N ₆ O ₂ Se ₂ ·1.5H ₂ O	C, H, N
137	D1	H	NH ₂ [S-(R*, R*)]	H	-	171 (dec)		

Diastereomers

^a Analyses for all listed elements within ±0.4%^b Noncrystalline^c High-resolution mass spectrum molecular ion^d Wieland T, Wieburg O, Fischer E, Korlein G, Annalen 1954;587:146^e Takase S, Uchida I, Tanaka H, Aoki H, Tetrahedron 1986;42:5879^f Palmisano G, Brenna E, Danieli B, Lesma G, Vodopivec B, Fiori G, Tet. Lett. 1990;31:7229^g Piotrowska H, Serafin B, Wejroch-Matacz K, Rocz. Chem. 1975;49:635-638.

-32-

EXAMPLES

The invention and the best mode for practicing the same are illustrated by the following Examples A-K.

5

EXAMPLE A

Preparation of Compounds 15, 17, 65, and 46 of Table 1 by the Method Outlined in Scheme 1

Concentrated HCl (16.6 mL) was added dropwise with stirring, over 10 minutes, to a solution of 4-(3-indolyl)butanoic acid [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOH$] (2.00 g) in DMSO (7.0 mL) at room temperature (method of Savige WE, Fontana A, J. Chem. Soc. Chem. Commun. 1976:599). After 15 minutes reaction, the mixture was diluted with water (80 mL) and extracted with EtOAc (4 x 100 mL). Removal of the solvent gave crude 4-(2-oxo-3-indoliny1)butanoic acid [III: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOH$] (2.07 g, 96%) as a green-brown solid; mp (water) 169-171°C (Hinman RL, Bauman CP, J. Org. Chem. 1964;29:1206 record mp 170-171°C).

Acetyl chloride (10 mL) was added dropwise with stirring to an ice-cooled solution of the above crude acid [III: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOH$] (2.05 g) in dry MeOH (50 mL), and the mixture stirred at 20°C for 18 hours. The solvent was removed, and repeated evaporation from MeOH yielded a brown oil, which was dissolved in $CHCl_3$ (100 mL) and washed with water (2 x 100 mL). Removal of the solvent gave crude methyl 4-(2-oxo-3-indoliny1)butanoate [III: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$] (2.20 g) as an oil. A pure sample was obtained by chromatography on silica gel and elution with EtOAc/light petroleum (1:2) as a pale yellow oil.

-33-

¹H NMR (CDCl₃): δ 8.82 (1H, s, NH), 7.24 (1H, d, J = 7.7 Hz, ArH), 7.21 (1H, t, J = 7.8 Hz, ArH), 7.03 (1H, td, J = 7.6, 0.8 Hz, ArH), 6.91 (1H, d, J = 7.7 Hz, ArH), 3.65 (3H, s, COOCH₃), 3.49 (1H, t, J = 6.0 Hz, H-3), 2.34 (2H, t, J = 7.5 Hz, CH₂CO), 2.00, 1.72 (4H, 2xm, 3-CH₂CH₂).

¹³C NMR (CDCl₃): δ 180.23 (s, CONH), 173.57 (s, COOCH₃), 141.54, 129.24 (2xs, Ar), 127.97, 124.11, 122.37, 109.80 (4xd, Ar), 51.53 (q, COOCH₃), 45.74 (d, C3), 33.83, 29.79, 21.18 (3xt, (CH₃)₃CO).

Analysis calculated for C₁₃H₁₅NO₃·H₂O requires:

C, 6.45; H, 6.7; N, 5.6%.

Found: C, 64.4; H, 6.5; N, 5.7%.

A solution of the above crude ester [III:

R₁ = R₃ = H, R₂ = (CH₂)₃COOMe] (0.48 g) in dry dioxane (10 mL) was treated with P₂S₅ (0.26 g) and NaHCO₃ (0.36 g), then the mixture was stirred under nitrogen at 95°C for 1 hour. The resulting solution was concentrated under reduced pressure, and the residue was diluted with CH₂Cl₂ (100 mL) and filtered. The filtrate was washed with water, solvent was removed, and the residue (0.55 g) was chromatographed on silica gel (elution with CH₂Cl₂) to give crude methyl 4-(2-thioxo-3-indoliny)butanoate [IV: R₁ = R₃ = H, R₂ = (CH₂)₃COOMe] (17) (0.18 g, 35%); mp (benzene-light petroleum) 109-110°C.

¹H NMR (CDCl₃): δ 10.59 (1H, s, NH), 7.31 (1H, d, J = 7.4 Hz, ArH), 7.27 (1H, td, J = 7.7, 0.9 Hz, ArH), 7.14 (1H, td, J = 7.5, 0.9 Hz, ArH), 7.02 (1H, d, J = 7.7 Hz, ArH), 3.85 (1H, t, J = 5.5 Hz, H-3), 3.64 (3H, s, COOCH₃), 2.32 (2H, t, J = 7.5 Hz, CH₂CO), 2.26, 2.15, 1.67, 1.46 (4H, 4xm, 3-CH₂CH₂).

¹³C NMR (CDCl₃): δ 207.80 (s, CSNH), 173.69 (s, COOCH₃), 143.27, 133.85 (2xs, ArH), 128.19, 124.17,

-34-

124.02, 110.12 (4xd, ArH), 57.36 (d, C-3), 51.61 (q, COOCH₃), 33.92, 32.76, 20.41 (3xt, (CH₂)₃CO).

Analysis calculated for C₁₃N₁₅NO₂S requires:

C, 62.6; H, 6.1; N, 5.6; S, 12.9%.

5 Found: C, 62.8; H, 5.9; N, 5.7; S, 12.9%.

A solution of 17 (0.39 g) in MeOH was exposed to air for 13 days, then the solvent was removed.

Chromatography of the residue on silica gel (elution with CH₂Cl₂) yielded bis[methylindolyl-3-butanoate-
10 (2)]-disulfide [V: R₁ = R₃ = H, R₂ = (CH₂)₃COOMe] (67) (0.31 g, 80%); mp (MeOH-dilute HCl) 91-93°C.

¹N NMR (CDCl₃): δ 8.19 (1H, s, NH), 7.57 (1H, d, J = 7.9 Hz, ArH), 7.28 (1H, d, J = 8.0 Hz, ArH), 7.24 (1H, ddd, J = 8.2, 7.1, 1.1 Hz, ArH), 7.12 (1H, ddd, J = 8.0, 6.9, 1.4 Hz, ArH), 3.56 (3H, s, COOCH₃), 2.67, 15 2.18 (2x2H, 2xt, J = 7.4 Hz, CH₂CH₂CH₂CO), 1.85 (2H, quin, J = 7.4 Hz, CH₂CH₂CH₂CO).

¹³C NMR (CDCl₃): δ 174.02 (s, COOCH₃), 137.29, 127.49, 125.99 (3xs, ArH), 124.21 (d, ArH), 123.70 (s, ArH), 20 119.95, 119.88, 111.08 (3xd, ArH), 51.42 (q, COOCH₃), 33.45, 25.67, 23.95 (3xt, (CH₂)₃CO).

Analysis calculated for C₂₆H₂₈N₂O₄S₂ requires:

C, 62.9; H, 5.7; N, 5.7; S, 12.9%.

Found: C, 62.6; H, 6.0; N, 5.5; S, 13.1%.

25 A mixture of 17 (0.26 g) in MeOH (10 mL) and K₂CO₃ (0.55 g) in water (3 mL) was stirred at room temperature for 2 days. NaBH₄ (100 mg) was then added, and the mixture stirred for 25 minutes, then diluted with water (100 mL) and extracted with CH₂Cl₂
30 (2 x 100 mL). The aqueous portion was acidified (to pH 3) with dilute HCl and extracted with EtOAc (3 x 100 mL). This extract was concentrated under reduced pressure, and the residue was crystallized from CH₂Cl₂-light petroleum to give 4-(2-thioxo-

-35-

3-indoliny)butanoic acid [IV: $R_1 = R_3 = H$,
 $R_2 = (CH_2)_3COOH$] (15) (30 mg, 12%); mp 132-134°C.

1H NMR (CD_3OD): δ 7.34 (1H, d, $J = 7.4$ Hz, ArH), 7.26 (1H, td, $J = 7.7, 1.1$ Hz, ArH), 7.12 (1H, td, $J = 7.5, 0.8$ Hz, ArH), 7.00 (1H, d, $J = 7.8$ Hz, ArH), 2.25 (2H, t, $J = 7.5$ Hz, CH_2COOH), 2.24, 2.10, 1.55, 1.33 (4H, 4xm, 3- CH_2CH).

Analysis calculated for $C_{12}H_{13}NO_2S$ requires:

C, 61.3; H, 5.6; N, 6.0; S, 13.6%

Found: C, 61.1; H, 6.2; N, 6.1; S, 13.5%.

Similar hydrolysis of 67 (at 30°C for 6 hours, then 20°C for 1 day) gave bis[indolyl-3-butanoic acid-(2)]disulfide [V: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOH$] (65) (30 mg, 20%); mp (aqueous MeOH) 141-143.5°C.

1H NMR (CD_3OD): δ 7.48 (1H, dt, $J = 8.0, 0.8$ Hz, ArH), 7.32 (1H, dt, $J = 8.2, 0.7$ Hz, ArH), 7.16 (1H, ddd, $J = 8.1, 7.1, 1.1$ Hz, ArH), 7.00 (1H, ddd, $J = 8.0, 7.1, 0.8$ Hz, ArH), 2.42 (2H, t, $J = 7.6$ Hz, CH_2CO), 1.93 (2H, t, $J = 7.3$ Hz, 3- CH_2), 1.58 (2H, quin, $J = 7.5$ Hz, $CH_2CH_2CH_2CO$).

^{13}C NMR (CD_3OD): δ 177.52 (s, COOH), 139.31, 128.69, 126.69, 124.84 (4xs, ArH), 124.67, 120.48, 120.27, 112.34 (4xd, ArH), 34.39, 27.24, 24.82 (3xt, $(CH_2)_3COOH$).

Analysis calculated for $C_{24}H_{24}N_2O_4S_2 \cdot H_2O$ requires:

C, 60.4; H, 5.2; N, 5.9; S, 13.4%.

Found: C, 60.4; H, 5.4; N, 5.9; S, 13.6%.

Compounds 7, 9, 36 and 39 of Table 1

Similar treatment of methyl 3-(3-indoliny)-propanoic [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2COOH$] (0.93 g) with DMSO/HCl, followed by esterification with diazomethane and chromatography on silica gel, gave methyl 3-(2-oxo-3-indolyl)propanoate [III: $R_1-R_3 = H$,

-36-

$R_2 = (\text{CH}_2)_2\text{COOMe}]$ (0.89 g, 89%) as a yellow oil

(Julian PL, Printy HC, J. Am. Chem. Soc.

1953;75:5301-5305 report mp 79-80°C).

^1H NMR (CDCl_3): δ 8.75 (1H, s, NH), 7.22 (2H, m, ArH),

5 7.03 (1H, ddd, $J = 7.8, 7.1, 1.1$ Hz, ArH), 6.91 (1H, dd, $J = 7.3, 1.3$ Hz, ArH), 3.63 (3H, s, OCH_3), 3.54 (1H, t, $J = 5.8$ Hz, H-3), 2.61-2.20 (4H, m, 3- CH_2CH_2).

Analysis calculated for $\text{C}_{12}\text{H}_{13}\text{NO}_3$ requires:

M+ 219.0895.

10 HREIMS m/z Found: M+ 219.0898.

Treatment of this ester [III: $R_1 = R_3 = \text{H}$,

$R_2 = (\text{CH}_2)_2\text{COOMe}]$ (0.89 g) with P_2S_5 as above, followed by chromatography on silica gel, eluting with EtOAc/light petroleum (3:1), gave an oil (0.44 g).

15 Crystallization from MeOH gave 2,2'-dithiobis[methyl 3-(3-indolyl)propanoate [V: $R_1 = R_3 = \text{H}$,

$R_2 = (\text{CH}_2)_2\text{COOMe}]$ (39) (61 mg, 6%); mp 162.5-164°C.

^1H NMR (CDCl_3): δ 8.21 (1H, s, NH), 7.55 (1H, dd, $J = 8.0, 0.7$ Hz, ArH), 7.25 (2H, m, ArH), 7.12 (1H, ddd, $J = 8.0, 5.4, 2.6$ Hz, ArH), 3.56 (3H, s, OCH_3), 2.98, 2.47 (2x2H, 2xt, $J = 7.9$ Hz, 3- CH_2CH_2).

20 ^{13}C NMR (CDCl_3): δ 173.38 (s, COOCH_3), 137.25, 127.21, 125.80 (3xs, Ar), 124.30 (d, Ar), 122.79 (s, Ar), 120.10, 119.59, 111.21 (3xd, Ar), 51.56 (q, OCH_3), 34.97 (t, CH_2CO), 20.27 (t, 3- CH_2).

25 Analysis calculated for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_4\text{S}_2$ requires:

C, 61.5; H, 5.2; N, 6.0; S, 13.7%.

Found: C, 61.4; H, 5.3; N, 6.1; S, 13.7%.

30 Crystallization of the mother liquor residue from benzene/light petroleum gave methyl 3-(2-thioxo-3-indolyl)propanoate [IV: $R_1 = R_3 = \text{H}$, $R_2 = (\text{CH}_2)_2\text{COOMe}]$ (9) (0.24 g, 25%); mp (CH_2Cl_2 /light petroleum) 96-98°C.

-37-

^1H NMR (CDCl_3): δ 9.83 (1H, s, NH), 7.29 (2H, m, ArH), 7.16 (1H, td, J = 7.5, 0.9 Hz, ArH), 6.99 (1H, d, J = 7.8 Hz, ArH), 3.91 (1H, t, J = 5.4 Hz, H-3), 3.60 (3H, s, OCH_3), 2.52 (2H, m, 3- CH_2), 2.42, 2.11 (2x1H, 2xm, CH_2CO).

^{13}C NMR (CDCl_3): δ 207.26 (s, CSNH), 173.37 (s, COOCH_3), 143.24, 133.08 (2xs, Ar), 128.43, 124.35, 124.09, 110.01 (4xd, Ar), 56.45 (d, C-3), 51.68 (q, OCH_3), 29.33, 28.19 (2xt, 3- CH_2CH_2).

Analysis calculated for $\text{C}_{12}\text{H}_{13}\text{NO}_2\text{S}$ requires:

C, 61.3; H, 5.6; N, 6.0; S, 13.6%.

Found: C, 61.4; H, 5.5; N, 6.0; S, 13.7%.

Hydrolysis of 9 with $\text{K}_2\text{CO}_3/\text{MeOH}/\text{H}_2\text{O}$ as described above, followed by chromatography on silica gel,

reduction with NaBH_4 and crystallization from

CH_2Cl_2 /isopropyl ether/light petroleum gave

3-(2-thioxo-3-indoliny)propanoic acid [IV:

$\text{R}_1 = \text{R}_3 = \text{H}$, $\text{R}_2 = (\text{CH}_2)_2\text{COOH}$] (7) (25 mg, 22%);

mp 170-173°C.

^1H NMR (CD_3COCD_3): δ 11.48 (1H, s, NH), 7.43 (1H, d, J = 7.4 Hz, ArH), 7.30 (1H, t, J = 7.7 Hz, ArH), 7.15 (1H, t, J = 7.4 Hz, ArH), 7.11 (1H, d, J = 7.8 Hz, ArH), 3.90 (1H, t, J = 5.3 Hz, H-3), 2.49 (1H, m, $\text{CH}_2\text{CH}_2\text{CO}$), 2.37 (2H, m, $\text{CH}_2\text{CH}_2\text{CO}$), 2.11 (1H, m, $\text{CH}_2\text{CH}_2\text{CO}$).

^{13}C NMR (CD_3COCD_3): δ 208.48 (s, CSNH), 174.14 (s, COOH), 145.18, 134.55 (2xs, Ar), 129.05, 125.08, 124.30, 110.87 (4xd, Ar), 57.18 (d, C-3), 29.86, 29.25 (2xt, $\text{CH}_2\text{CH}_2\text{COOH}$).

Analysis calculated for $\text{C}_{11}\text{H}_{11}\text{NO}_2\text{S}$ requires:

C, 59.71; H, 5.01; N, 6.33%.

Found: C, 59.49; H, 4.97; N, 6.15%.

Aerial oxidation of 7 in MeOH at 20°C for 12 days, followed by dilution with water, gave

-38-

bis[indolyl-3-propanoic acid-(2)]disulfide [V:

$R_1 = R_3 = H$, $R_2 = (CH_2)_2COOH$] (36) (30 mg, 30%);

mp (aqueous MeOH) 118-120.5°C.

1H NMR (CD_3OD): δ 7.47 (1H, dt, $J = 8.0$, 0.8 Hz, ArH),

5 7.30 (1H, dt, $J = 8.1$, 0.8 Hz, ArH), 7.15 (1H, ddd,
 $J = 8.1$, 7.1, 1.0 Hz, ArH), 7.00 (1H, ddd, $J = 8.0$,
 7.1, 0.9 Hz, ArH), 2.74, 2.2 (2x2H, 2xt, $J = 8.0$ Hz,
 $(CH_2)_2COOH$).

^{13}C NMR (CD_3OD): δ 176.95 (s, COOH), 139.26, 128.26

10 126.65 (3xs, Ar), 124.69 (d, Ar), 123.66 (s, Ar),
 120.36, 120.20, 112.41 (3xd, Ar), 36.29, 21.22 (2xt,
 $(CH_2)_2COOH$).

Analysis calculated for $C_{22}H_{20}N_2O_4S_2 \cdot H_2O$ requires:

C, 57.6; H, 4.8; N, 6.1; S, 14.0%.

15 Found: C, 57.6; H, 5.0; N, 6.1; S, 13.9%.

Compounds 3 and 27 of Table 1

Similar reaction of methyl 2-(2-oxo-3-indoliny)-

acetate [III: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$: Takase S,

20 Uchida I, Tanaka H, Aoki H, Tetrahedron 1986;42:5879]

(0.13 g) with P_2S_5 gave methyl 2-(2-thioxo-

3-indoliny)acetate [IV: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$]

(3) (50 mg, 36%); mp (MeOH) 150-152°C.

1N NMR ($CDCl_3$): δ 10.36 (1H, s, NH), 7.29 (1H, d,

25 $J = 7.6$ Hz, ArH), 7.27 (1H, t, $J = 7.8$ Hz, ArH), 7.11
 (1H, t, $J = 7.6$ Hz, ArH), 7.00 (1H, d, $J = 7.8$ Hz,
 ArH), 4.14 (1H, dd, $J = 8.4$, 4.2 Hz, H-3), 3.72 (3H, s,
 $COOCH_3$), 3.35 (1H, dd, $J = 17.0$, 4.2 Hz, CH_2CO), 2.88
 (1H, dd, $J = 17.0$, 8.5 Hz, CH_2CO).

30 ^{13}C NMR ($CDCl_3$): δ 206.59 (s, CSNH), 171.53 (s,

$COOCH_3$), 143.10, 133.53 (2xs, ArH), 128.45, 124.20,
 124.12, 110.07 (4xd, ArH), 53.53 (d, C3), 52.02 (q,
 $COOCH_3$), 37.94 (t, CH_2).

-39-

Analysis calculated for $C_{11}H_{11}NO_2S$ requires:

C, 59.7; H, 5.0; N, 6.3; S, 14.5%.

Found: C, 59.9; H, 5.3; N, 6.4; S, 14.4%.

A solution of 3 (0.10 g) in benzene-light petroleum (1:1, 30 mL) exposed to air for 2 days gave a quantitative yield of bis[methylindolyl-3-acetate-(2)]-disulfide [V: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$] (Compound 27 of Table I); mp (benzene/light petroleum) 160-162°C.

1N NMR ($CDCl_3$): δ 8.69 (1H, s, NH), 7.52 (1H, dd, $J = 8.2, 0.6$ Hz, ArH), 7.21 (1H, ddd, $J = 8.2, 6.6, 1.1$ Hz, ArH), 7.12 (2H, m, ArH), 3.83 (2H, s, CH_2CO), 3.71 (3H, s, $COOCH_3$).
 ^{13}C NMR ($CDCl_3$): δ 172.54 (s, $COOCH_3$), 137.20, 127.19, 127.03 (3xs, ArH), 124.26, 120.31, 119.45 (3xd, ArH), 116.23 (s, ArH), 111.41 (d, ArH), 52.25 (q, OCH_3), 30.51 (t, CH_2CO).

Analysis calculated for $C_{22}H_{20}N_2O_4S_2$ requires:

C, 60.0; H, 4.6; N, 6.4; S, 14.6%.

Found: C, 60.0; H, 4.8; N, 6.3; S, 14.4%.

Additional amounts of 27 were also obtained from the mother liquors of the P_2S_5 reaction.

Compounds 8, 11, 37, and 40 of Table 1

A solution of 18-crown-6 (0.44 g), potassium t-butoxide (2.20 g) and methyl 3-(3-indolyl)propanoate [II: $R_1 = R_3 = H$; $R_2 = (CH_2)_2COOMe$] (3.24 g) in dry benzene (20 mL) was stirred at 20°C for 15 minutes, then cooled in ice. A solution of CH_3I (3.42 g) in benzene (10 mL) was added, then the flask was sealed and the mixture stirred at 20°C for 1 day (method of Guida WC, Mathre DJ, J. Org. Chem. 1980;45:3172). The resulting solution was filtered to remove salts, washing with CH_2Cl_2 , then the combined filtrates washed

-40-

with water and the solvents removed. Chromatography on silica gel, eluting with CH_2Cl_2 /light petroleum (1:1), gave methyl 3-(1-methyl-3-indolyl)propanoate

[II: $\text{R}_1 = \text{H}$; $\text{R}_3 = \text{Me}$; $\text{R}_2 = (\text{CH}_2)_2\text{COOMe}$] (1.90 g, 52%) as a colorless oil (Snyder HR, Eliel EL, J. Am. Chem. Soc. 1949;71:663-669 report oil, $\text{bp}_{0.25}$ 180-190°C).

^1H NMR (CDCl_3): δ 7.58 (1H, dt, $J = 7.7, 0.9$ Hz, ArH), 7.28 (1H, dt, $J = 7.9, 1.3$ Hz, ArH), 7.21 (1H, ddd, $J = 8.1, 6.7, 1.3$ Hz, ArH), 7.10 (1H, ddd, $J = 7.9, 6.5, 1.5$ Hz, ArH), 6.86 (1H, s, H-2), 3.73, 3.67 (2x3H, 2xs, NCH_3 , OCH_3), 3.09, 2.70 (2x2H, 2xt, $J = 7.6$ Hz, 3- CH_2CH_2).

Analysis calculated for $\text{C}_{13}\text{H}_{15}\text{NO}_2$ requires:

$\text{M}^+ 217.1103$.

15 HREIMS m/z Found: $\text{M}^+ 217.1101$.

Oxidation of the ester [II: $\text{R}_1 = \text{H}$; $\text{R}_3 = \text{Me}$; $\text{R}_2 = (\text{CH}_2)_2\text{COOMe}$] (1.85 g) with DMSO/HCl as above for 3 hours gave crude 3-(1-methyl-2-oxo-3-indoliny)-propanoic acid [III: $\text{R}_1 = \text{H}$; $\text{R}_2 = \text{Me}$; $\text{R}_3 = (\text{CH}_2)_2\text{COOH}$] (2.08 g) as a colorless oil.

^1H NMR (CD_3OD): δ 7.31 (2H, m, ArH), 7.09 (1H, td, $J = 8.0, 1.0$ Hz, ArH), 6.98 (1H, d, $J = 7.6$ Hz, ArH), 3.56 (1H, t, $J = 6.1$ Hz, H-3), 3.20 (3H, s, NCH_3), 2.41-2.15 (4H, m, 3- CH_2CH_2).

25 ^{13}C NMR (CD_3OD): δ 179.64 (s, COOH), 176.55 (s, CONCH₃), 145.52, 129.73 (2xs, Ar), 129.39, 125.00, 123.93, 109.64 (4xd, Ar), 45.79 (d, C-3), 31.01, 26.91 (2xt, 3- CH_2CH_2), 26.44 (q, NCH_3).

Analysis calculated for $\text{C}_{12}\text{H}_{13}\text{NO}_3$ requires:

30 $\text{M}^+ 219.0895$.

HREIMS m/z Found: $\text{M}^+ 219.0897$.

This was esterified with diazomethane as above, then the product chromatographed on silica gel. Elution with EtOAc/light petroleum (1:2) gave methyl

-41-

3-(1-methyl-2-oxo-3-indoliny)propanoate [III: $R_1 = H$; $R_2 = Me$; $R_3 = (CH_2)_2COOMe$] (1.40 g, 70%) as a colorless oil.

1H NMR ($CDCl_3$): δ 7.27 (2H, m, ArH), 7.06 (1H, td, $J = 7.5, 0.8$ Hz, ArH), 6.83 (1H, d, $J = 7.7$ Hz, ArH), 3.62 (3H, s, OCH_3), 3.50 (1H, t, $J = 6.0$ Hz, H-3), 3.20 (3H, s, NCH_3), 2.52-2.18 (4H, m, CH_2CH_2).

^{13}C NMR ($CDCl_3$): δ 177.23 (s, $CONCH_3$), 173.38 (s, $COOCH_3$), 144.36 (s, Ar), 128.20 (d, Ar), 128.11 (s, Ar), 123.92, 122.48, 108.06 (3xd, Ar), 51.64 (q, OCH_3), 44.36 (d, C-3), 30.12 (t, CH_2OCO), 26.14 (q, NCH_3), 25.64 (t, 3- CH_2).

Analysis calculated for $C_{13}H_{15}NO_3$ requires:

M+ 233.1052.

HREIMS m/z Found: M+ 233.1055.

Treatment of this ester [III: $R_1 = H$; $R_2 = Me$; $R_3 = (CH_2)_2COOMe$] (1.38 g) with P_2S_5 as above followed by chromatography on silica gel, eluting with CH_2CH_2 /light petroleum (3:2), gave methyl 3-(1-methyl-2-thioxo-3-indoliny)propanoate [IV: $R_1 = H$; $R_2 = Me$; $R_3 = (CH_2)_2COOMe$] (11) (1.40 g, 95%); mp (benzene/light petroleum) 71-73°C.

1H NMR ($CDCl_3$): δ 7.35 (2H, m, ArH), 7.19 (1H, td, $J = 7.5, 0.9$ Hz, ArH), 7.00 (1H, d, $J = 7.7$ Hz, ArH), 3.92 (1H, t, $J = 5.4$ Hz, H-3), 3.63, 3.58 (2x3H, 2xs, NCH_3 , OCH_3), 2.53 (2H, m, 3- CH_2), 2.34, 2.03 (2x1H, 2xm, CH_2CO).

^{13}C NMR ($CDCl_3$): δ 204.77 (s, $CSNCH_3$), 173.32 (s, $COOCH_3$), 145.89, 132.37 (2xs, Ar), 128.40, 124.31, 123.99, 109.51 (4xd, Ar), 56.26 (d, C-3), 51.61 (q, OCH_3), 31.35 (q, NCH_3), 29.31, 28.46 (2xt, 3- CH_2CH_2).

Analysis calculated for $C_{13}H_{15}NO_2S$ requires:

C, 62.6; H, 6.1; N, 5.6; S, 12.9%.

Found: C, 62.7; H, 6.3; N, 5.7; S, 13.0%.

-42-

Oxidation of (11) (0.70 g) with FeCl_3 (0.70 g) in $\text{EtOAc}/\text{CH}_2\text{Cl}_2$, chromatography of the product on silica gel, and elution with CH_2Cl_2 gave 2,2'-dithiobis[methyl 3-(1-methyl-3-indolyl)propanoate] [V: $R_1 = \text{H}$; $R_2 = \text{Me}$; $R_2 = (\text{CH}_2)_2\text{COOMe}$] (40) (0.38 g, 54%); mp ($\text{CH}_2\text{Cl}_2/\text{MeOH}$) 139-141.5°C.

^1H NMR (CDCl_3): δ 7.49 (1H, d, $J = 8.0$ Hz, ArH), 7.27 (1H, ddd, $J = 8.3, 6.1, 0.9$ Hz, ArH), 7.25 (1H, d, $J = 8.1$ Hz, ArH), 7.09 (1H, ddd, $J = 8.0, 6.1, 1.9$ Hz, ArH), 3.59, 3.53 (2x3H, 2xs, NCH_3 , OCH_3), 2.76, 2.21 (2x2H, 2xt, $J = 7.8$ Hz, 3- CH_2CH_2).

^{13}C NMR (CDCl_3): δ 173.17 (s, COOCH_3), 138.49, 127.00, 126.09 (3xs, Ar), 124.14 (d, Ar), 123.77 (s, Ar), 119.68, 119.65, 109.87 (3xd, Ar), 51.39 (q, OCH_3), 35.09 (t, CH_2CO), 29.86 (q, NCH_3), 20.50 (t, 3- CH_2).

Analysis calculated for $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_4\text{S}_2$ requires:

C, 62.9; H, 5.7; N, 5.7; S, 12.9%.

Found: C, 62.6; H, 5.6; N, 5.5; S, 13.0%.

A solution of (11) (0.53 g) in EtOH (10 mL) and 2N aqueous NaOH (3 mL) was stirred at 20°C for 80 minutes. The mixture was then diluted with water (100 mL) and extracted with CH_2Cl_2 (100 mL). The aqueous portion was adjusted to pH 2 with dilute HCl and extracted with EtOAc (3 x 120 mL). The EtOAc extracts were washed with water (150 mL) and the solvent removed under reduced pressure to give a yellow oil (0.48 g). This was redissolved in MeOH (7 mL) and 2 M aqueous NaOH (1 mL) and treated with NaBH (150 mg) for 5 minutes at 20°C. The mixture was then quenched with water and worked up as before to give a pale brown oil (0.46 g). Crystallization from $\text{CH}/\text{light petroleum}$ gave 3-(1-methyl-2-thioxo-3-indolyl)propanoic acid [$R_1 = \text{H}$; $R_2 = \text{Me}$; $R_3 = (\text{CH}_2)_2\text{COOH}$] (8) (0.32 g, 60%); mp 126-128.5°C.

-43-

¹H NMR (CDCl₃): δ 7.35 (2H, m, ArH), 7.18 (1H, td, J = 7.5, 0.9 Hz, ArH), 7.00 (1H, d, J = 7.8 Hz, ArH), 3.93 (1H, t, J = 5.3 Hz, H-3), 3.63 (3H, s, NCH₃), 2.51 (2H, m, 3-CH₂), 2.38 (1H, ddd, J = 16.1, 9.3, 6.7 Hz, CHCO), 2.06 (1H, ddd, J = 16.0, 9.8, 6.1 Hz, CHCO).

¹³C NMR (CDCl₃): δ 204.61 (s, CSNCH₃), 178.41 (COOH), 145.88, 132.24 (2xs, Ar), 128.50, 124.38, 123.96, 109.57 (4xd, Ar), 56.05 (d, C-3), 31.37 (q, NCH₃), 29.16, 28.16 (2xt, 3-CH₂CH₂).

Analysis calculated for C₁₂H₁₃NO₂S·0.25H₂O requires:

C, 60.1; H, 5.6; N, 5.8; S, 13.4%.

Found: C, 60.0; H, 5.6; N, 5.9; S, 13.4%.

Similar hydrolysis of 40 (0.37 g) in EtOH/2 M aqueous NaOH for 3 hours at 20°C gave, after workup, a yellow oil (0.30 g). Crystallization from AcOH gave 2,2'-dithiobis[3-(1-methyl-3-indolyl)propanoic acid] [V: R₁ = H; R₂ = (CH₂)₂COOH; R₃ = Me] (37) (73 mg, 20%); mp 158.5-160°C.

¹H NMR ((CD₃)₂CO): δ 7.59 (1H, d, J = 8.1 Hz, ArH), 7.39 (1H, d, J = 8.0 Hz, ArH), 7.27 (1H, ddd, J = 8.2, 7.1, 0.9 Hz, ArH), 7.07 (1H, ddd, J = 8.1, 7.1, 0.8 Hz, ArH), 3.60 (3H, s, NCH₃), 2.79, 2.31 (2x2H, 2xt, J = 7.9 Hz, 3-CH₂CH₂).

¹³C NMR ((CD₃)₂CO): δ 173.75 (s, COOH), 139.61, 127.54, 127.06 (3xs, Ar), 125.08 (d, Ar), 125.02 (s, Ar), 120.55, 120.53, 110.03 (3xd, Ar), 35.56 (t, CH₂CO), 30.13 (q, NCH₃), 21.32 (t, 3-CH₂).

Analysis calculated for C₂₄H₂₄N₂O₄S₂ requires:

C, 61.5; H, 5.2; N, 6.0; S, 13.7%.

Found: C, 61.5; H, 5.2; N, 6.1; S, 13.6%.

Chromatography of the mother liquors on silica gel, then treatment with NaBH₄ as above and crystallization of the products from CH₂Cl₂/light

-44-

petroleum also gave 3-(1-methyl-2-thioxo-3-indoliny)-propanoic acid (8) (0.12 g, 32%).

Compounds 16, 18, 66, and 68 of Table 1

5 N-Alkylation of methyl 4-(3-indolyl)butanoate
[III: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$] (2.14 g), with
18-crown-6 (0.26 g), potassium t-butoxide/ CH_3I as above
gave methyl 4-(1-methyl-3-indolyl)butanoate

10 [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$, $R_3 = Me$] (0.92 g,
40%) as a brown oil, which was used directly.
 1H NMR ($CDCl_3$): δ 7.58 (1H, dt, $J = 7.9, 0.9$ Hz, ArH),
7.28 (1H, d, $J = 8.2$ Hz, ArH), 7.21 (1H, ddd, $J = 8.1,$
7.0, 1.1 Hz, ArH), 7.09 (1H, ddd, $J = 8.0, 7.0, 1.0$ Hz,
15 ArH), 6.84 (1H, s, ArH), 3.74 (3H, s, NCH_3), 3.66 (3H,
s, $COOCH_3$), 2.79, 2.38 (2x2H, 2xt, $J = 7.4$ Hz,
 $CH_2CH_2CH_2CO$), 2.03 (2H, quin, $J = 7.4$ Hz, $CH_2CH_2CH_2CO$).
 ^{13}C NMR ($CDCl_3$): δ 174.21 (s, $COOCH_3$), 137.08, 127.84
(2xs, ArH), 126.34, 121.50, 118.98, 118.62 (4xd, ArH),
114.07 (s, ArH), 109.13 (d, ArH), 51.44 (q, $COOCH_3$),
20 33.68 (t, CH_2CO), 32.55 (q, NCH_3), 25.58, 24.41 (2xt,
3- CH_2CH_2).

HREIMS m/z Found: M^+ 231.1259.

4-(3-Indolyl)butanoic acid (1.04 g, 52%) was
recovered by dissolving the filtered precipitates from
25 the above reaction in water and acidifying;
mp 124-126°C (Jackson RW, Manske RH, J. Am. Chem. Soc.
1930;52:5029 record mp 124°C).

Reaction of the ester [II: $R_1 = R_3 = H$,
 $R_2 = (CH_2)_3COOMe$, $R_3 = Me$] with DMSO/ HCl as above gave
30 crude 4-(1-methyl-2-oxo-3-indoliny)butanoic acid

[III: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$, $R_3 = Me$] (0.84 g,
91% yield) as a brown oil.

1H NMR ($CDCl_3$): δ 7.28 (1H, td, $J = 7.7, 0.9$ Hz, ArH),
7.25 (1H, d, $J = 7.7$ Hz, ArH), 7.06 (1H, td, $J = 7.5,$

-45-

0.9 Hz, ArH), 6.83 (1H, d, $J = 7.8$ Hz, ArH), 3.47 (1H, t, $J = 5.9$ Hz, H-3), 3.21 (3H, s, NCH₃), 2.37 (2H, t, $J = 7.4$ Hz, CH₂CO), 2.00, 1.69 (2x2H, 2xm, 3-CH₂CH₂).

An ice-cooled solution of the above crude oxoacid
5 [III: R₁ = R₃ = H, R₂ = (CH₂)₃COOMe, R₃ = Me] (0.84 g) in ether (10 mL) was treated, dropwise with stirring, with an ethereal solution of diazomethane (from N-nitrosomethylurea, 1.2 g). After 30 minutes at 20°C, the solvent was removed under reduced pressure, and the
10 residue was chromatographed on silica gel (elution with EtOAc/light petroleum (1:2)) to give methyl 4-(1-methyl-2-oxo-3-indoliny)butanoate [III: R₁ = R₃ = H, R₂ = (CH₂)₃COOMe, R₃ = Me] (0.64 g, 72%); mp (EtOAc/light petroleum) 69-71°C.

15 ¹H NMR (CDCl₃): δ 7.28 (1H, t, $J = 7.8$ Hz, ArH), 7.26 (1H, d, $J = 7.6$ Hz, ArH), 7.05 (1H, td, $J = 7.6$, 0.7 Hz, ArH), 6.82 (1H, d, $J = 7.7$ Hz, ArH), 3.64 (3H, s, COOCH₃), 3.44 (1H, t, $J = 6.0$ Hz, H-3), 3.20 (3H, s, NCH₃), 2.33 (2H, t, $J = 7.5$ Hz, CH₂CO), 1.98, 1.68
20 (2x2H, 2xm, 3-CH₂CH₂).

¹³C NMR (CDCl₃): δ 177.52 (s, CONCH₃), 173.59 (s, COOCH₃), 144.38, 128.71 (2xs, ArH), 128.00, 123.84, 122.40, 108.02 (4xd, ArH), 51.54 (q, COOCH₃), 45.26 (d, C-3), 33.89, 29.98 (2xt, CH₂CH₂CH₂CO), 26.15 (q, NCH₃),
25 21.30 (t, 3-CH₂CH₂).

Analysis calculated for C₁₄H₁₇NO₃ requires:

C, 68.0; H, 6.9; N, 5.7%.

Found: C, 67.9; H, 6.7; N, 5.7%.

The above oxoester [III: R₁ = R₃ = H,
30 R₂ = (CH₂)₃COOMe, R₃ = Me] (0.90 g) was treated with P₂S₅ as above, followed by workup and chromatography on silica gel. Elution with CH₂Cl₂/light petroleum (3:2) gave methyl 4-(1-methyl-2-thioxo-3-indolyl)butanoate

-46-

[IV: $R_1 = H$, $R_2 = (CH_2)_3COOMe$, $R_3 = Me$] (18) (1.07 g, 79%); mp (benzene-light petroleum) 103-106°C.

1H NMR ($CDCl_3$): δ 7.34 (2H, m, ArH), 7.19 (1H, td, $J = 8.0, 0.9$ Hz, ArH), 7.00 (dd, $J = 8.0, 2.3$).

5 Analysis calculated for $C_{14}H_{17}NO_2S$ requires:

C, 63.9; H, 6.5; N, 5.3; S, 12.2%.

Found: C, 64.0; H, 6.4; N, 5.3; S, 12.3%.

A solution of 18 (0.47 g) in EtOAc (7 mL) was stirred with $FeCl_3$ (0.43 g) for 1 hour at 20°C, then worked up and chromatographed on silica gel. Elution with CH_2Cl_2 gave bis[methyl 1-methylindolyl-3-butanoate-(2)]disulfide [V: $R_1 = H$, $R_2 = (CH_2)_3COOMe$, $R_3 = Me$] (68) (0.40 g, 85%); mp (CH_2Cl_2 /MeOH) 112-113°C.

15 1H NMR ($CDCl_3$): δ 7.52 (1H, d, $J = 8.0$ Hz, ArH), 7.28 (1H, ddd, $J = 8.2, 6.0, 1.0$ Hz, ArH), 7.25 (1H, d, $J = 8.0$ Hz, ArH), 7.09 (1H, ddd, $J = 8.0, 6.0, 1.9$ Hz, ArH), 3.59, 3.55 (2x3H, 2xs, NCH_3 , $COOCH_3$), 2.42, 2.07 (2x2H, 2xt, $J = 7.4$ Hz, $CH_2CH_2CH_2CO$), 1.68 (2H, quin, $J = 7.4$ Hz, $CH_2CH_2CH_2CO$).

20 ^{13}C NMR ($CDCl_3$): δ 173.82 (s, $COOCH_3$), 138.47, 127.23, 126.43, 124.74 (4xs, ArH), 124.05, 119.90, 119.49, 109.72 (4xd, ArH), 51.35 (q, $COOCH_3$), 33.40 (t, CH_3CO), 29.82 (q, NCH_3), 25.83, 24.17 (2xt, 3- CH_2CH_2).

25 Analysis calculated for $C_{28}H_{32}N_2O_4S_2$ requires:

C, 64.1; H, 6.1; N, 5.3; S, 12.2%.

Found: C, 63.9; H, 6.4; N, 5.3; S, 12.1%.

Hydrolysis of 18 with EtOH/ H_2O /NaOH, followed by treatment with $NaBH_4$ and crystallization from CH_2Cl_2 /light petroleum, as above, gave 4-(1-methyl-2-thioxo-3-indolyl)butanoic acid [IV: $R_1 = H$, $R_2 = (CH_2)_3COOH$, $R_3 = Me$] (16) (0.18 g, 44%); mp 144-146.5°C.

-47-

^1H NMR (CDCl_3): δ 7.34 (2H, m, ArH), 7.18 (1H, t, $J = 7.6$ Hz, ArH), 7.00 (1H, d, $J = 7.7$ Hz, ArH), 3.85 (1H, t, $J = 5.5$ Hz, H-3), 3.63 (3H, s, NCH_3), 2.34, 2.07 (2H, t, $J = 7.6$ Hz, CH_2CO), 2.28 2.18, 1.59, 1.40 (4x1H, 4xm, 3- CH_2CH_2).

^{13}C NMR (CDCl_3): δ 205.31 (s, CSNCH_3), 178.62 (s, COOH), 145.81, 133.06 (2xs, Ar), 128.20, 124.30, 123.86, 109.54 (4xd, Ar), 57.14 (d, C-3), 33.77, 33.01 (2xt, 3- $\text{CH}_2\text{CH}_2\text{CH}_2$), 31.42 (q, NCH_3), 20.11 (t, 3- CH_2CH_2).

Analysis calculated for $\text{C}_{13}\text{H}_{15}\text{NO}_2\text{OS}\cdot\text{H}_2\text{O}$ requires:

C, 61.6; H, 6.7; N, 5.5; S, 12.7%.

Found: C, 61.9; H, 6.3; N, 5.6; S, 12.8%.

Similar hydrolysis of 68 (0.40 g) gave, after workup, a yellow oil (0.37 g). Chromatography on silica gel, eluting with EtOAc/light petroleum (1:2) containing 1% AcOH, gave an oil (0.25 g).

Crystallization from AcOH then gave 2,2'-dithiobis[4-(1-methyl-3-indolyl)butanoic acid] [V: $\text{R}_1 = \text{H}$, $\text{R}_2 = (\text{CH}_2)_3\text{COOH}$, $\text{R}_3 = \text{Me}$] (66) (0.17 g, 42%); mp 106.5-109.5°C.

^1H NMR (CDCl_3): δ 7.51 (1H, d, $J = 8.0$ Hz, ArH), 7.27 (2H, m, ArH), 7.08 (1H, ddd, $J = 8.0, 6.0, 2.0$ Hz, ArH), 3.55 (3H, s, NCH_3), 2.44 2.12 (2x2H, 2xt, $J = 7.4$ Hz, 3- $\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}$), 1.68 (2H, quintet, $J = 7.4$ Hz, 3- $\text{CH}_2\text{CH}_2\text{CH}_2$).

^{13}C NMR (CDCl_3): δ 179.32 (s, COOH), 138.49, 127.49, 126.43, 124.56 (4xs, Ar), 124.14, 119.86, 119.62, 109.79 (4xd, Ar), 33.37 9t, CH_2CO), 29.86 (q, NCH_3) 25.59, 24.13 (2xt, 3- CH_2CH_2).

Analysis calculated for $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_4\text{S}_2\cdot 2\text{CH}_3\text{COOH}$ requires:

C, 58.4; H, 5.9; N, 4.5; S, 10.4%.

Found: C, 58.4; H, 5.9; N, 4.5; S, 10.6%.

-48-

EXAMPLE B

Preparation of Compounds 1, 29, 30, and 31 of Table 1
by the Method Outlined in Scheme 2

5 A solution of purified S_2Cl_2 (0.50 mL) in THF
(20 mL) was added dropwise to a stirred, ice-cooled
solution of 3-indolylacetic acid [II: $R_1 = R_3 = H$,
 $R_2 = CH_2COOH$] (2.20 g) in dry THF (30 mL) (method of
Wieland T, Wieburg O, Fischer E, Korlein G, Annalen
1954;587:146). After 30 minutes at 20°C the solvent
10 was removed, and the residue was crystallized from
aqueous acetic acid to give a yellow solid (1.00 g).
Recrystallization of this solid from aqueous MeOH,
followed by further crystallization from EtOAc-benzene
gave bis[indolyl-3-acetic acid-(2)]trisulfide [VI:
15 $R_1 = R_3 = H$, $R_2 = CH_2COOH$, $n = 3$] (30) as a yellow
powder (80 mg, 3%); mp 199-202°C.
 1H NMR (CD_3COCD_3): δ 10.18 (1H, s, NH), 7.59 (1H, m,
ArH), 7.06 (2H, m, ArH), 6.82 (1H, m, ArH), 3.99 (2H,
s, CH_2CO).
20 ^{13}C NMR (CD_3COCD_3): δ 173.30 (s, COOH), 138.82,
128.26, 127.03 (3xs, ArH), 124.76, 120.60, 120.33 (3xd,
ArH), 116.97 (s, ArH), 112.16 (d, ArH), 30.89 (t,
 CH_2CO).
Analysis calculated for $C_{20}H_{16}N_2O_4S_3$ requires:
25 C, 54.1; H, 3.6; N, 6.3; S, 21.6%.
Found: C, 54.1; H, 3.8; N, 6.0; S, 21.2%.
The mother liquors from the above aqueous methanol
crystallization were evaporated, and the resulting
solid was recrystallized from CH_2Cl_2 to give
30 bis[indolyl-3-acetic acid-(2)]disulfide [VI:
 $R_1 = R_3 = H$, $R_2 = CH_2COOH$, $n = 2$] (29) as a yellow
solid (0.19 g, 7%); mp 196-199°C (Wieland T, Wieburg O,
Fischer E, Korlein G, Annalen 1954;587:146 record
mp 208°C).

-49-

- ¹H NMR (CD₃COCD₃): δ 10.62 (1H, s, NH), 7.58 (1H, dd, J = 8.1, 0.6 Hz, ArH), 7.42 (1H, dt, J = 8.2, 0.8 Hz, ArH), 7.23 (1H, ddd, J = 8.2, 7.1, 0.9 Hz, ArH), 7.09 (1H, ddd, J = 8.0, 7.1, 0.9 Hz, ArH), 3.55 (2H, s, CH₂CO).
- ¹³C NMR (CD₃COCD₃): δ 172.67 (s, COOH), 138.78, 128.33, 127.86 (3xs, ArH), 124.79, 120.72, 120.56 (3xd, ArH), 117.78 (s, ArH), 112.41 (d, ArH), 30.67 (t, CH₂CO).
- Analysis calculated for C₂₀H₁₆N₂O₄S₂ requires:
C, 58.2; H, 3.9; N, 6.8; S, 15.5%.
Found: C, 57.6; H, 4.4; N, 6.6; S, 15.3%.
- Methylation of crude 30 with diazomethane as described above, followed by chromatography on silica gel, gave bis[methylindolyl-3-acetate-(2)]trisulfide [VI: R₁ = R₃ = H, R₂ = CH₂COOMe, n = 3] (31) (0.16 g, 47%); mp (CH₂Cl₂-light petroleum) 130-132°C.
- ¹H NMR (CDCl₃): δ 8.76 (1H, s, NH), 7.40 (1H, d, J = 8.0 Hz, ArH), 6.99 (1H, ddd, J = 8.0, 7.1, 0.9 Hz, ArH), 6.88 (1H, ddd, J = 8.2, 7.1, 0.9 Hz, ArH), 6.41 (1H, d, J = 8.2 Hz, ArH), 3.93 (2H, s, CH₂CO), 3.78 (3H, s, COOCH₃).
- ¹³C NMR (CDCl₃): δ 172.93 (s, COOCH₃), 137.66, 127.02, 125.80 (3xs, ArH), 124.29, 120.06, 118.46 (3xd, ArH), 114.61 (s, ArH), 111.15 (d, ArH), 52.40 (q, COOCH₃), 30.30 (t, CH₂CO).
- Analysis calculated for C₂₂H₂₀N₂O₄S₃ requires:
C, 55.9; H, 4.2; N, 5.9; S, 20.3%.
Found: C, 55.6; H, 4.4; N, 5.8; S, 19.9%.
- Reduction of 29 with NaBH₄/K₂CO₃/MeOH as above gave 2-(2-thioxo-3-indoliny)acetic acid [IV: R₁ = R₃ = H; R₂ = CH₂COOH] (1) (58 mg, 34%); mp (EtOAc/light petroleum) 166-168°C (Wieland T,

-50-

Wieburg O, Fischer E, Korlein G, Annalen 1954;587:146
record mp 170-171°C).

5 ^1H NMR ($(\text{CD}_3)_2\text{CO}$): δ 11.51 (1H, s, NH), 7.39 (1H, d, $J = 7.9$ Hz, ArH), 7.29 (1H, td, $J = 7.7, 0.8$ Hz, ArH), 7.11 (2H, m, ArH), 4.02 (1H, dd, $J = 3.9, 8.4$ Hz, H-3), 3.36 (1H, dd, $J = 17.2, 3.9$ Hz, 3-CH), 2.83 (1H, dd, $J = 17.2, 8.4$ Hz, 3-CH).

Compounds 4 and 28 of Table 1

10 Methyl 2-(1-methyl-3-indolyl)acetate [II: $R_1 = \text{H}$;
 $R_2 = \text{CH}_2\text{COOMe}$; $R_3 = \text{Me}$] (Guida WC, Mathre DJ, J. Org.
Chem. 1980;45:3172-3176) (1.18 g) was treated with
15 S_2Cl_2 (0.25 mL) as above and the product then
chromatographed on silica gel. Elution with
 CH_2Cl_2 /light petroleum (2:1) and CH_2Cl_2 gave a yellow
oil, from which crystallization with EtOAc/light
petroleum gave 2,2'-monothiobis[methyl 2-(1-methyl-
3-indolyl)acetate] [VI: $R_1 = \text{H}$, $R_2 = \text{CH}_2\text{COOMe}$;
 $R_3 = \text{Me}$; $n = 1$] (0.17 g, 13%); mp 155-156°C.

20 ^1H NMR (CDCl_3): 7.54 (1H, d, $J = 8.0$ Hz, ArH), 7.22
(2H, m, ArH), 7.11 (1H, ddd, $J = 8.0, 4.9, 3.0$ Hz,
ArH), 3.96 (2H, s, 3- CH_2), 3.61 (3H, s, OCH_3), 3.48
(3H, s, NCH_3).

25 ^{13}C NMR (CDCl_3): 171.54 (s, COOCH_3), 137.80, 126.80,
126.24 (3xs, Ar), 123.03, 119.92, 118.96 (3xd, Ar),
112.95 (s, Ar), 109.37 (d, Ar), 51.85 (q, OCH_3), 31.04
(t, 3- CH_2), 30.38 (q, NCH_3).

Analysis calculated for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$ requires:

C, 66.1; H, 5.5; N, 6.4; S, 7.3%.

30 Found: C, 65.9; H, 5.6; N, 6.4; S, 7.4%.

Further crystallization of mother liquor fractions
from benzene/light petroleum gave 2,2'-dithiobis[methyl
2-(1-methyl-3-indolyl)acetate] [VI: $R_1 = \text{H}$,

-51-

$R_2 = \text{CH}_2\text{COOMe}$; $R_3 = \text{Me}$; $n = 2$] (28) (0.16 g, 13%);

mp 130-132.5°C.

^1H NMR (CDCl_3): 7.51 (1H, dt, $J = 8.0, 0.8$ Hz, ArH),
7.29 (2H, m, ArH), 7.12 (1H, ddd, $J = 8.0, 6.0, 2.0$ Hz,
5 ArH), 3.57 (3H, s, OCH_3), 3.48 (3H, s, NCH_3), 3.33 (2H,
s, 3- CH_2).

^{13}C NMR (CDCl_3): 171.44 (s, COOCH_3), 138.42, 128.13,
126.38 (3xs, Ar), 124.37, 120.13, 120.08 (3xd, Ar),
117.48 (s, Ar), 109.94 (d, Ar), 51.79 (q, OCH_3), 30.57
10 (q, NCH_3), 29.96 (t, 3- CH_2).

Analysis calculated for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_4\text{S}_2$ requires:

C, 61.5; H, 5.1; N, 6.0; S, 13.7%.

Found: C, 61.4; H, 5.2; N, 6.0; S, 13.8%.

The remaining mother liquor was treated
15 successively with NaBH_4 and FeCl_3 as above, to give an
additional 0.36 g (26%) of 28.

Reduction of 28 with NaBH_4 as above gave methyl
2-(1-methyl-2-thioxo-3-indoliny)acetate [IV: $R_1 = \text{H}$;
 $R_2 = \text{CH}_2\text{COOMe}$; $R_3 = \text{Me}$] (4) (61%); mp (benzene/light
20 petroleum) 68-70°C.

^1H NMR (CDCl_3): 7.34 (2H, m, ArH), 7.16 (1H, td,
 $J = 7.5, 0.9$ Hz, ArH), 7.01 (1H, d, $J = 7.8$ Hz, ArH),
4.15 (1H, dd, $J = 8.7, 4.1$ Hz, H-3), 3.71 (3H, s,
 OCH_3), 3.65 (3H, s, NCH_3), 3.40 (1H, dd, $J = 17.0,$
25 4.1 Hz, 3-CH), 2.83 (1H, dd, $J = 17.0, 8.7$ Hz, 3-CH).

^{13}C NMR (CDCl_3): 204.24 (s, CSNCH_3), 171.68 (s,
 COOCH_3), 145.74, 132.95 (2xs, Ar), 128.47, 124.40,
123.96, 109.54 (4xd, Ar), 53.41 (d, C-3), 51.96 (q,
 OCH_3), 38.46 (t, 3- CH_2), 31.57 (q, NCH_3).

30 Analysis calculated for $\text{C}_{12}\text{H}_{13}\text{NO}_2\text{S}$ requires:

C, 61.3; H, 5.6; N, 6.0; S, 13.6%.

Found: C, 61.5; H, 5.8; N, 6.2; S, 13.9%.

-52-

Compounds 2 and 32 of Table 1

- Similar treatment of 1-methyl-3-indolylacetic acid
[II: $R_1 = H$, $R_2 = CH_2COOH$, $R_3 = Me$] (Guida WC,
Mathre DJ, J. Org. Chem. 1980;45:3172; Kaestle KL,
5 Anwer MK, Audhya TK, Goldstein G, Tetrahedron Lett.
1991;32:327) with S_2Cl_2 followed by chromatography on
silica gel gave bis[1-methylindolyl-3-acetic acid-(2)]-
disulfide [VI: $R_1 = R_3 = H$, $R_2 = CH_2COOH$, $n = 2$] (32)
10 (0.10 g, 8%); mp (Me_2CO /light petroleum) 190-192.5°C
(Wieland T, Wieburg O, Fischer E, Korlein G, Annalen
1954;587:146 record mp 190-191°C).
 1H NMR (CD_3COCD_3): δ 7.56 (1H, dt, $J = 8.1, 0.9$ Hz,
ArH), 7.44 (1H, d, $J = 8.3$ Hz, ArH), 7.31 (1H, ddd,
 $J = 8.2, 7.0, 1.2$ Hz, ArH), 7.11 (1H, ddd, $J = 8.0,$
15 7.0, 0.9 Hz, ArH), 3.65 (3H, s, NCH_3), 3.23 (2H, s,
 CH_2CO).
 ^{13}C NMR (CD_3COCD_3): δ 172.21 (s, COOH), 139.52,
128.56, 127.45 (3xs, ArH), 125.21, 120.91, 120.74 (3xd,
ArH), 119.38 (s, ArH), 111.04 (d, ArH), 30.81 (t,
20 CH_2CO), 30.31 (q, NCH_3).
Analysis calculated for $C_{22}H_{20}N_2O_2S_2$ requires:
C, 60.0; H, 4.6; N, 6.4; S, 14.5%.
Found: C, 59.4; H, 4.9; N, 6.4; S, 15.0%.
Reduction of 32 with $NaBH_4/K_2CO_3/MeOH$ as above
25 gave 2-(1-methyl-2-thioxo-3-indolyl)acetic acid [IV:
 $R_1 = H$; $R_2 = CH_2COOH$; $R_3 = Me$] (2) (62 mg, 60%);
mp (CH_2Cl_2 /light petroleum) 150-153°C (Wieland T,
Wieburg O, Fischer E, Korlein G, Annalen 1954;587:146
record mp 149-150°C).
30 1H NMR ($CDCl_3$): δ 7.37 (2H, m, ArH), 7.18 (1H, t,
 $J = 7.5$ Hz, ArH), 7.02 (1H, d, $J = 7.8$ Hz, ArH), 4.14
(1H, dd, $J = 8.6, 3.9$ Hz, H-3), 3.65 (3H, s, NCH_3),
3.48 (1H, dd, $J = 17.5, 4.0$ Hz, 3-CH), 2.86 (1H, dd,
 $J = 17.5, 8.7$ Hz, 3-CH).

-53-

^{13}C NMR (CDCl_3): δ 203.88 (s, CSNCH_3), 176.31 (s, COOH), 145.67, 132.64 (2xs, Ar), 128.57, 124.52, 124.00, 109.59 (4xd, Ar), 53.07 (d, C-3), 38.33 (t, 3- CH_2), 31.59 (q, NCH_3).

5

Compounds 6 and 34 of Table 1

N-Benzyl 3-indolylacetamide [II: $\text{R}_1 = \text{R}_3 = \text{H}$, $\text{R}_2 = \text{CH}_2\text{CONHCH}_2\text{Ph}$] (Katritzky AR, J. Chem. Soc. 1955:2581) (1.48 g) was treated with S_2Cl_2 as above, and the product mixture was treated with NaBH_4 (ca. 0.7 g) in EtOH (10 mL) for 30 minutes at 20°C , then diluted with water (100 mL), acidified with dilute HCl and extracted in CH_2Cl_2 (2 x 100 mL) and EtOAc (100 mL). A sample from evaporation of the combined
15 extracts was crystallized from EtOAc-light petroleum to give N-benzyl (2-thioxo-3-indolinyl)acetamide [IV: $\text{R}_1 = \text{R}_3 = \text{H}$, $\text{R}_2 = \text{CH}_2\text{CONHCH}_2\text{Ph}$] (6) (0.12 g, 7%); mp $193\text{--}195^\circ\text{C}$.

^1H NMR (CD_3SOCD_3): δ 12.64 (1H, s, NH), 8.50 (1H, t, $\text{J} = 5.9$ Hz, NHCH_2), 7.32 (2H, t, $\text{J} = 7.3$ Hz, ArH), 7.25 (3H, m, ArH), 7.11 (1H, d, $\text{J} = 7.3$ Hz, ArH), 7.00 (1H, t, $\text{J} = 8.0$ Hz, ArH), 6.53 (1H, m, ArH), 4.34, 4.28 (2x1H, 2xdd, $\text{J} = 15.3, 5.9$ Hz, NHCH_2), 4.04 (1H, dd, $\text{J} = 9.5, 4.2$ Hz, H-3), 3.10 (1H, dd, $\text{J} = 15.3, 4.2$ Hz, CH_2CO), 2.47 (1H, dd, $\text{J} = 15.3, 9.5$ Hz, CH_2CO).
20

^{13}C NMR (CD_3SOCD_3): δ 206.62 (s, CSNH), 169.41 (s, CONH), 143.97, 139.24, 134.36 (3xs, ArH), 128.22 (2xd, ArH), 127.95 (d, ArH), 127.36 (2xd, ArH), 126.77, 123.91, 123.09, 110.10 (4xd, ArH), 53.94 (d, C-3),
25 42.27, t, NHCH_2), 39.19 (t, CH_2CO).
30

Analysis calculated for $\text{C}_{17}\text{H}_{10}\text{N}_2\text{OS}$ requires:

C, 68.9; H, 5.4; N, 9.5; S, 10.8%.

Found: C, 68.8; H, 5.8; N, 9.5; S, 10.7%.

-54-

The remaining product mixture (1.60 g) was treated with FeCl_3 as above then chromatographed on silica gel to give a yellow oil (1.40 g). Crystallization from EtOAc/light petroleum then EtOAc gave

5 2,2'-dithiobis[N-benzyl 2-(3-indolyl)acetamide]

[VI: $R_1 = R_3 = \text{H}$; $R_2 = \text{CH}_2\text{CONHCH}_2\text{Ph}$] (34) (0.36 g, 22%); mp 200.5-203.5°C.

^1H NMR ($\text{CD}_3)_2\text{SO}$): δ 11.57 (1H, s, CSNH), 8.45 (1H, t, $J = 5.9$ Hz, NHCH_2), 7.53 (1H, d, $J = 8.0$ Hz, ArH), 7.30 (1H, d, $J = 8.2$ Hz, ArH), 7.29-7.14 (6H, m, ArH), 7.01 (1H, t, $J = 7.5$ Hz, ArH), 4.19 (2H, d, $J = 5.9$ Hz, NHCH_2), 3.44 (2H, s, 3- CH_2).

10 ^{13}C NMR ($\text{CD}_3)_2\text{SO}$): δ 170.08 (9s, CONH), 139.36, 137.42 (2xs, Ar), 128.12, 127.13 (4xd, Ar), 127.12, 126.82 (2xs, Ar), 126.63, 123.41, 119.67, 119.09 (4xd, Ar), 116.83 (s, Ar), 111.43 (d, Ar), 42.25 (t, NHCH_2), 31.73 (t, 3- CH_2).

Analysis calculated for $\text{C}_{34}\text{H}_{30}\text{N}_4\text{O}_2\text{S}_2$ requires:

C, 62.6; H, 6.1; N, 5.6; S, 12.9%.

20 Found: C, 62.7; H, 6.3; N, 5.7; S, 13.0%.

Compounds 13 and 47 of Table 1

Esterification of 3-(3-indolyl)propanoic acid

25 [II: $R_1 = R_2 = \text{H}$, $R_3 = (\text{CH}_2)_2\text{COOH}$] (1.50 g) with diazomethane as above gave methyl 3-(3-indolyl)-propanoate [II: $R_1 = R_2 = \text{H}$, $R_3 = (\text{CH}_2)_2\text{COOMe}$] (1.62 g, 100%) as a light brown oil. This was stirred with benzylamine (5 mL) at 140°C for 4 hours (Katritzky AR, J. Chem. Soc. 1955:2581-2586) to give, after workup and

30 chromatography on silica gel, N-benzyl 3-(3-indolyl)-propanamide [II: $R_1 = R_2 = \text{H}$; $R_3 = (\text{CH}_2)_2\text{CONHCH}_2\text{Ph}$] (1.81 g, 88%); mp (EtOAc/light petroleum) 125-126.5°C.

^1H NMR (CDCl_3): 8.05 (1H, s, NH), 7.59 (1H, d, $J = 7.8$ Hz, ArH), 7.34 (1H, d, $J = 7.9$ Hz, ArH), 7.24

-55-

(3H, m, ArH), 7.18 (1H, dd, $J = 7.9, 7.2$ Hz, ArH), 7.10 (1H, dd, $J = 7.9, 7.2$ Hz, ArH), 7.07 (2H, m, ArH), 6.93 (1H, d, $J = 1.9$ Hz, H-2), 5.64 (1H, t, $J = 5.7$ Hz, NHCH₂), 4.35 (2H, d, $J = 5.7$ Hz, 2 H, NHCH₂), 3.13, 2.59 (2x2H, 2xt, $J = 7.3$ Hz, 3-CH₂CH₂).

¹³C NMR (CDCl₃): 172.54 (s, CONH), 138.20, 136.35 (2xs, Ar), 128.58, 127.66 (4xd, Ar), 127.35 (d, Ar), 127.08 (s, Ar), 122.04, 121.88, 119.35, 118.68 (4xd, Ar), 113.79 (s, Ar), 111.21 (d, Ar), 43.51 (t, NHCH₂), 37.42 (t, CH₂CO), 21.38 (t, 3-CH₂).

Analysis calculated for C₁₈H₁₈N₂O requires:

C, 77.7; H, 6.6; N, 10.1%.

Found: C; 77.4; H, 6.5; N, 10.3%.

The above amide [II: R₁ = R₂ = H, R₃ = (CH₂)₂CONHCH₂Ph] (1.74 g) was treated with S₂Cl₂, and the product mixture was treated successively with NaBH₄ and FeCl₃ as above, then chromatographed on silica gel. Elution with EtOAc/light petroleum (2:1) gave 2,2'-monothiobis[N-benzyl 3-(3-indolyl)-propanamide] [VI: R₁ = R₂ = H; R₃ = (CH₂)₂CONHCH₂Ph; n = 1] (0.10 g, 6%); mp (CH₂Cl₂/light petroleum) 218-219°C.

¹H NMR (CD₃)₂SO): 11.01 (1H, s, CSNH), 8.38 (1H, t, $J = 5.7$ Hz, NHCH₂), 7.56 (1H, d, $J = 7.9$ Hz, ArH), 7.26-7.03 (7H, 2xm, ArH), 6.97 (1H, t, $J = 7.5$ Hz, ArH), 4.26 (2H, d, $J = 5.5$ Hz, NHCH₂), 3.22, 2.55 (2x2H, 2xt, $J = 7.6$ Hz, 3-CH₂CH₂).

Analysis calculated for C₃₆H₃₄N₄O₂S·H₂O requires:

C, 72.6; H, 5.9; N, 9.4; S, 5.4%.

Found: C, 72.7; H, 5.9; N, 9.6; S, 5.7%.

Further elution with EtOAc/light petroleum (1:1) gave a yellow oil (1.10 g) from which crystallization with benzene/CH₂Cl₂/light petroleum gave 2,2'-dithiobis[N-benzyl 3-(3-indolyl)propanamide]

-56-

[VI: $R_1 = R_2 = H$, $R_3 = (CH_2)_2CONHCH_2Ph$; $n = 2$] (47)
(0.73 g, 38%); mp (CH_2Cl_2 /light petroleum) 141-144°C.
 1H NMR ($CDCl_3$): 8.47 (1H, s, CSNH), 7.51 (1H, d,
5 $J = 7.9$ Hz, ArH), 7.27-7.20 (4H, m, ArH), 7.13 (1H,
ddd, $J = 8.2, 7.1, 1.1$ Hz, ArH), 7.00 (3H, m, ArH),
5.01 (1H, t, $J = 5.7$ Hz, $NHCH_2$), 4.16 (2H, d, t,
 $J = 5.7$ Hz, $NHCH_2$), 2.88, 1.87 (2x2H, 2xt, $J = 7.7$ Hz,
3- CH_2CH_2).

10 ^{13}C NMR ($CDCl_3$): 171.93 (s, CONH), 138.30, 137.27
(2xs, Ar), 128.51, 127.78 (4xd, Ar), 127.30 (d, Ar),
127.07, 125.66 (2xs, Ar), 124.43 (d, Ar), 123.93 (s,
Ar), 120.18, 119.94, 111.23 (3xd, Ar), 43.39 (t,
 $NHCH_2$), 37.09 (t, CH_2CO), 20.56 (t, 3- CH_2).

Analysis calculated for $C_{36}H_{34}N_4O_2S_2$ requires:

15 C, 69.9; H, 5.5; N, 9.1; S, 10.3%.

Found: C, 69.7; H, 5.6; N, 9.1; S, 10.5%.

Reduction of 47 with $NaBH_4$ as above gave a
quantitative yield of N-benzyl 3-(2-thioxo-

3-indoliny)propanamide [IV: $R_1 = R_3 = H$,
20 $R_2 = (CH_2)_2CONHCH_2Ph$] (13); mp (CH_2Cl_2) 149.5-151°C.
 1H NMR ($(CD_3)_2CO$): 11.46 (1H, s, CSNH), 7.45 (1H, t,
 $J = 6.0$ Hz, $NHCH_2$), 7.42 (1H, d, $J = 7.9$ Hz, ArH),
7.32-7.16 (6H, m, ArH), 7.13 (1H, td, $J = 7.5, 0.9$ Hz,
ArH), 7.09 (1H, d, $J = 7.8$ Hz, ArH), 4.37, 4.33 (2x1H,
25 2xdd, $J = 15.0, 6.0$ Hz, $NHCH_2$), 3.87 (1H, t,
 $J = 5.4$ Hz, H-3), 2.56, 2.34, 2.04 (4H, 3xm, 3- CH_2CH_2).
 ^{13}C NMR ($(CD_3)_2CO$): 208.79 (s, CSNH), 172.23 (s,
CONH), 145.20, 140.69, 134.88 (3xs, Ar), 129.14 (d, 2e,
Ar), 128.93 (d, Ar), 128.33 (d, 2e, Ar), 127.62,
30 125.27, 124.22, 110.78 (4xd, Ar), 57.57 (d, C-3), 43.46
(t, $NHCH_2$), 31.87, 30.09 (2xt, 3- CH_2CH_2).

Analysis calculated for $C_{18}H_{18}N_2OS$ requires:

C, 67.7; H, 6.0; N, 8.8; S, 10.0%.

Found: C, 67.3; H, 5.9; N, 8.9; S, 10.5%.

-57-

Compound 69 of Table 1

3-(3-Indolyl)butanoic acid [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOH$] (1.10 g) was esterified with excess ethereal diazomethane to give methyl

- 5 4-(3-indolyl)butanoate [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_3COOMe$] (1.17 g, 100%); mp 73-75°C (Jackson RW, Manske RH, J. Am. Chem. Soc. 1930;52:5029 record mp 73-74°C). This was stirred with benzylamine (5 mL) at 150°C for 4 hours to give, after
- 10 chromatography on silica gel (eluting with 1:4 EtOAc:CH₂Cl₂), N-benzyl-4-(3-indolyl)butanamide [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_3CONHCH_2Ph$] (1.43 g, 90%); mp (CH₂Cl₂/light petroleum) 123-124°C.

- ¹H NMR (CDCl₃): δ 8.05 (1H, br s, NH), 7.58 (1H, d, $J = 7.9$ Hz, ArH), 7.37-7.23 (6H, m, ArH), 7.18 (1H, ddd, $J = 8.1, 7.1, 1.0$ Hz, ArH), 7.10 (1H, ddd, $J = 8.0, 7.0, 0.9$ Hz, ArH), 6.95 (1H, d, $J = 1.7$ Hz, H-2), 5.68 (1H, br t, $J = 5.7$ Hz, NHCH₂), 4.42 (1H, d, $J = 5.7$ Hz, NHCH₂), 2.82 (2H, t, $J = 7.3$ Hz, 3-CH₂),
- 15 2.27 (2H, t, $J = 7.5$ Hz, CH₂CO), 2.09 (2H, pentet, $J = 7.3$ Hz, 3-CHCH₂).

- ¹³C NMR (CDCl₃): δ 172.79 (s, CONH), 138.35, 136.33 (2xs, Ar), 128.69, 127.84 (2d, 2x2C, Ar), 127.49 (d, Ar), 127.46 (s, Ar), 121.91, 121.50, 119.83, 118.3 (4xd, Ar), 115.57 (s, Ar), 111.10 (d, Ar), 43.58 (t, NCH₂), 36.15 (t, CH₂CO), 26.06, 24.48 (2xt, 3-CH₂CH₂).
- 25

Analysis calculated for C₁₉H₂₀N₂O requires:

C, 78.1; H, 6.9; N, 9.6%.

Found: C, 77.8; H, 6.8; N, 9.7%.

- 30 The above amide (1.38 g) was treated with S₂Cl₂ as above, then the product mixture obtained after workup was treated with NaBH₄ as described above. The resulting oil was oxidized with 35% H₂O₂ (0.50 mL) in MeOH (10 mL) at 20°C for 20 minutes. Dilution with

-58-

water, extraction in CH_2Cl_2 , and evaporation gave an oil which was chromatographed on silica gel. Elution with EtOAc/light petroleum (3:5) gave

2,2'-thiobis[N-benzyl-4-(3-indolyl)butanamide]

5 [VI: $n = 1$; $R_1 = R_3 = \text{H}$, $R_2 = (\text{CH}_2)_3\text{CONHCH}_2\text{Ph}$] (0.14 g, 10%); mp (CH_2Cl_2 /light petroleum) 105.5-108°C (dec).

^1H NMR (CDCl_3): δ 10.25 (1H, s, NH), 7.49 (1H, d, $J = 8.0$ Hz, ArH), 7.35-7.25 (6H, m, ArH), 7.11 (1H, ddd, $J = 8.2, 7.0, 1.2$ Hz, ArH), 7.01 (1H, ddd, $J = 7.9, 7.0, 0.9$ Hz, ArH), 5.75 (1H, t, $J = 5.6$ Hz, NHCH_2), 4.38 (2H, d, $J = 5.7$ Hz, NHCH_2), 3.07 (2H, t, $J = 7.8$ Hz, 3- CH_2), 2.38 (2H, t, $J = 6.3$ Hz, CH_2CO), 2.13 (2H, m, 3- CH_2CH_2).

10 ^{13}C NMR (CDCl_3): δ 173.49 (s, CONH), 138.12, 136.97 (2xs, Ar), 128.73, 127.93 (2xd, 2x2C, Ar), 127.56 (d, Ar), 127.48, 124.00 (2xs, Ar), 122.53 (d, Ar), 119.79 (s, Ar), 119.07, 118.60, 111.52 (3xd, Ar), 43.79 (t, NCH_2), 35.66 (t, CH_2CO), 25.77, 24.38 (2xt, 3- CH_2CH_2).

Analysis calculated for $\text{C}_{38}\text{H}_{38}\text{N}_4\text{O}_2\text{S}$ requires:

20 C, 74.3; H, 6.2; N, 9.1; S, 5.2%.

Found: C, 74.2; H, 6.1; N, 9.1; S, 5.0%.

Elution with EtOAc:light petroleum (1:1) gave

2,2'-dithiobis[N-benzyl-4-(3-indolyl)butanamide] (69)

25 [VI: $n = 2$; $R_1 = R_3 = \text{H}$, $R_2 = (\text{CH}_2)_3\text{CONHCH}_2\text{Ph}$] (0.55 g, 36%); mp (CH_2Cl_2 /benzene) 98.5-101°C (dec).

^1H NMR ($(\text{CD}_3)_2\text{CO}$): δ 10.48 (1H, s, NH), 7.58 (1H, d, $J = 8.0$ Hz, ArH), 7.38 (1H, d, $J = 8.2$ Hz, ArH), 7.37 (1H, m, NHCH_2), 7.30-7.15 (6H, m, ArH), 7.03 (1H, ddd, $J = 7.9, 7.3, 0.7$ Hz, ArH), 4.30 (2H, d, $J = 6.0$ Hz, NHCH_2), 2.67 (2H, t, $J = 7.6$ Hz, 3- CH_2), 2.09 (2H, t, $J = 7.5$ Hz, CH_2CO), 1.84 (2H, pentet, $J = 7.5$ Hz, 3- CH_2CH_2).

30 ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$): δ 172.93 (s, CONH), 140.80, 138.83 (2xs, Ar), 129.12 (d, 2C, Ar), 128.46 (s, Ar), 128.35

-59-

(d, 2C, Ar), 127.58 (d, Ar), 126.71, 124.54, (2xs, Ar), 124.46, 120.60, 120.13, 112.36 (4xd, Ar), 43.43 (t, NCH₂), 36.34 (t, CH₂CO), 27.75, 24.95 (2xt, 3-CH₂CH₂).

Analysis calculated for C₃₈H₃₈N₄O₂S₂ requires:

5 C, 70.6; H, 5.9; N, 8.7; S, 9.9%.

Found: C, 70.4; H, 6.0; N, 8.8; S, 9.8%.

Compound 35 of Table 1

3-Indolylacetonitrile [II: R₁ = R₃ = H, R₂ = CH₂CN] (1.00 g) was treated with S₂Cl₂ as above, then the product mixture obtained after workup was treated with NaBH₄ as described above. Crystallization of the resulting oil from CH₂Cl₂ gave

2,2'-thiobis[3-indolylacetonitrile] [VI: n = 1; R₁ = R₃ = H, R₂ = CH₂CN] (0.11 g, 10%); mp 237-240°C (Piotrowska H, Serafin B, Wejroch-Matacz K, Rocz. Chem. 1975;49:635 record mp 242-244°C).

¹H NMR ((CD₃)₂SO): δ 11.61 (1H, s, NH), 7.65 (1H, d, J = 8.0 Hz, ArH), 7.37 (1H, d, J = 8.2 Hz, ArH), 7.20 (1H, ddd, J = 8.0, 7.1, 0.9 Hz, ArH), 7.10 (1H, ddd, J = 8.0, 7.1, 0.8 Hz, ArH), 4.26 (2H, s, 3-CH₂).

¹³C NMR: δ 136.52, 125.99, 123.92 (3xs, Ar), 123.25, 119.78 (2xd, Ar), 118.67 (s, Ar), 118.48, 111.60 (2xd, Ar), 108.78 (s, 3-CH₂CN), 12.98 (t, 3-CH₂).

25 Analysis calculated for C₂₀H₁₄N₄S·0.5H₂O requires:

C, 68.4; H, 4.3; N, 16.0; S, 9.2%.

Found: C, 68.4; H, 4.2; N, 16.2; S, 9.1%.

The mother liquor was oxidized with H₂O₂ in MeOH as above, then the resulting solid was chromatographed on silica gel, eluting with CH₂Cl₂, to give 2,2'-dithiobis[3-indolylacetonitrile] (35) [VI: n = 2; R₁ = R₃ = H, R₂ = CH₂CN] (0.62 g, 52%); mp (CH₂Cl₂/MeOH) 168.5-169.5°C (Piotrowska H, Serafin B,

-60-

Wejroch-Matacz K, Rocz. Chem. 1975;49:635 record
mp 169-170°C).

¹H NMR ((CD₃)₂SO): δ 11.90 (1H, s, NH), 7.67 (1H, d,
J = 8.1 Hz, ArH), 7.42 (1H, d, J = 8.2 Hz, ArH), 7.28
5 (1H, ddd, J = 8.1, 7.1, 1.0 Hz, ArH), 7.14, (1H, ddd,
J = 8.0, 7.1, 0.8 Hz, ArH), 3.69 (2H, s, 3-CH₂).

¹³C NMR: δ 137.28, 126.36, 125.82 (3xs, Ar), 124.26,
120.03, 119.11, (3xd, Ar), 118.10 (s, Ar), 112.03 (d,
Ar), 111.66 (s, 3-CH₂CN), 12.56 (t, 3-CH₂).

10 Analysis calculated for C₂₀H₁₄N₄S₂ requires:

C, 64.2; H, 3.7; N, 15.0; S, 17.1%.

Found: C, 64.1; H, 3.9; N, 15.1; S, 17.0%.

Compound 48 of Table 1

15 3-Indolylpropionitrile [II: R₁ = R₃ = H,
R₂ = (CH₂)₂CN] (Reppe W, Ufer H, German patent 698,273)
(1.00 g) was treated with S₂Cl₂ as above, then the
product mixture obtained after workup was treated
successively with NaBH₄, then H₂O₂ as described above.
20 The resulting oil was chromatographed on silica gel,
eluting with CH₂Cl₂, to give 2,2'-thiobis[3-indolyl-
propionitrile] [VI: n = 1; R₁ = R₃ = H, R₂ = (CH₂)₂CN]
(43 mg, 4%); mp (CH₂Cl₂/light petroleum) 204.5-207°C
(Piotrowska H, Serafin B, Wejroch-Matacz K, Rocz. Chem.
25 1975;49:635 record mp 198-200°C).

¹H NMR ((CD₃)₂SO): δ 11.25 (1H, s, NH), 7.61 (1H, d,
J = 7.9 Hz, ArH), 7.31 (1H, d, J = 7.8 Hz, ArH), 7.13
(1H, dd, J = 8.0, 7.1 Hz, ArH), 7.02 (1H, dd, J = 7.9,
7.1 Hz, ArH), 3.23, 2.71 (2x2H, 2xt, J = 7.2 Hz,
3-CH₂CH₂).

30 ¹³C NMR: δ 136.65, 126.58, 124.04 (3xs, Ar), 122.65
(d, Ar), 120.36 (s, CN), 119.25, 118.79 (2xd, Ar),
116.32 (s, Ar), 111.31 (d, Ar), 20.60, 17.98 (2xt,
3-CH₂CH₂).

-61-

Further elution with CH_2Cl_2 gave
2,2'-dithiobis[3-indolylpropionitrile] (48)
[VI: $n = 2$; $R_1 = R_3 = \text{H}$, $R_2 = (\text{CH}_2)_2\text{CN}$] (0.82 g, 69%);
mp (CH_2Cl_2) 167-169°C (Piotrowska H, Serafin B,
5 Wejroch-Matacz K, Rocz. Chem. 1975;49:635 record
mp 165-167°C).
 ^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 11.71 (1H, s, NH), 7.59 (1H, d,
 $J = 8.0$ Hz, ArH), 7.38 (1H, dt, $J = 8.2$, 0.8 Hz, ArH),
7.22 (1H, ddd, $J = 8.2$, 7.1, 1.1 Hz, ArH), 7.04 (1H,
10 ddd, $J = 8.0$, 7.1, 0.9 Hz, ArH), 2.57, 2.37 (2x2H, 2xt,
 $J = 7.2$ Hz, 3- CH_2CH_2).
 ^{13}C NMR: δ 137.48, 126.16, 125.59 (3xs, Ar), 123.88
(d, Ar), 120.39, 119.87 (2xs, Ar, CN), 119.45, 111.64
(2xd, Ar), 19.80, 17.97 (2xt, 3- CH_2CH_2).

15

Compound 49 of Table 1

A solution of gramine (8.4 g) and methyl
nitroacetate (11.5 g) in xylene (50 mL) was stirred
under nitrogen at 90-100°C for 5 hours (method of
20 Lyttle DA, Weisblat DI, J. Am. Chem. Soc.
1947;69:2118). Evaporation gave an oil which was
chromatographed on silica gel, eluting with
 CH_2Cl_2 :light petroleum (1:1), to give
3-(2-nitroethyl)indole [II: $R_1 = R_3 = \text{H}$,
25 $R_2 = (\text{CH}_2)_2\text{NO}_2$] (4.44 g, 48%); mp (benzene/light
petroleum) 57-59.5°C (Somei M, Karasawa Y, Kaneko C,
Heterocycles 1981;16:941 record mp (MeOH) 54-55°C).
 ^1H NMR (CDCl_3): δ 8.05 (1H, br s, NH), 7.57 (1H, d,
 $J = 7.9$ Hz, ArH), 7.37 (1H, dt, $J = 8.2$, 0.8 Hz, ArH),
30 7.22 (1H, ddd, $J = 8.1$, 7.0, 1.1 Hz, ArH), 7.16 (1H,
ddd, $J = 7.9$, 7.1, 0.9 Hz, ArH), 7.04 (1H, d,
 $J = 2.4$ Hz, H-2), 4.66 (2H, t, $J = 7.3$ Hz, 3- CH_2CH_2),
3.49 (2H, td, $J = 7.3$, 0.6 Hz, 3- CH_2).

-62-

^{13}C NMR: δ 136.25, 126.67 (2xs, Ar), 122.56, 122.54, 119.91, 118.13, 111.45 (5xd, Ar), 110.05 (s, Ar), 75.73 (t, 3-CH₂CH₂), 23.63 (t, 3-CH₂).

5 The above nitroethyl compound (1.50 g) was treated with S₂Cl₂ as above, then the product mixture obtained after workup was treated successively with NaBH₄ then H₂O₂ as described above. The resulting oil was chromatographed on silica gel, eluting with CH₂Cl₂:light petroleum (4:3), to give

10 2,2'-thiobis[3-(2-nitroethyl)indole] [VI: n = 1; R₁ = R₃ = H, R₂ = (CH₂)₂NO₂] (49 mg, 3%); mp (CH₂Cl₂/light petroleum) 134.5-136°C.

^1H NMR ((CD₃)₂SO): δ 11.26 (1H, s, NH), 7.59 (1H, d, J = 7.9 Hz, ArH), 7.30 (1H, d, J = 8.1 Hz, ArH), 7.13 (1H, ddd, J = 8.1, 7.1, 0.9 Hz, ArH), 7.02 (1H, ddd, J = 7.9, 7.1, 0.8 Hz, ArH), 4.71 (2H, t, J = 7.3 Hz, 3-CH₂CH₂), 3.57 (2H, t, J = 7.3 Hz, 3-CH₂).

15 ^{13}C NMR: δ 136.59, 126.60, 124.20 (3xs, Ar), 122.56, 119.27, 118.43 (3xd, Ar), 113.37 (s, Ar), 111.24 (d, Ar), 75.11 (t, 3-CH₂CH₂), 22.69 (t, 3-CH₂).

20 Analysis calculated for C₂₀H₁₈N₄O₄S requires:

C, 58.5; H, 4.4; N, 13.7; S, 7.8%.

Found: C, 58.3; H, 4.7; N, 13.6; S, 8.0%.

Further elution as above gave

25 2,2'-dithiobis[3-(2-nitroethyl)indole] (49) [VI: n = 2; R₁ = R₃ = H, R₂ = (CH₂)₂NO₂] (1.28 g, 73%); mp (CH₂Cl₂/light petroleum) 153-154°C.

^1H NMR ((CD₃)₂SO): δ 11.68 (1H, s, NH), 7.57 (1H, d, J = 8.0 Hz, ArH), 7.36 (1H, d, J = 8.2 Hz, ArH), 7.21 (1H, ddd, J = 8.1, 7.1, 0.9 Hz, ArH), 7.04 (1H, ddd, J = 7.9, 7.1, 0.8 Hz, ArH), 4.41 (2H, t, J = 7.2 Hz, 3-CH₂CH₂), 2.97 (2H, t, J = 7.2 Hz, 3-CH₂).

30

-63-

^{13}C NMR: δ 137.37, 126.18, 125.95 (3xs, Ar), 123.76, 119.50, 119.08 (3xd, Ar), 117.39 (s, Ar), 111.59 (d, Ar), 75.05 (t, 3-CH₂CH₂), 22.06 (t, 3-CH₂).

Analysis calculated for C₂₀H₁₈N₄O₄S₂·0.5H₂O requires:

5 C, 53.2; H, 4.2; N, 12.4; S, 14.2%.

Found: C, 53.4; H, 4.2; N, 12.6; S, 14.0%.

Compounds 14 and 50 of Table 1

10 DEPC (98%, 1.28 mL) was added to a stirred solution of 3-(3-indolyl)propanoic acid [II: R₁ = R₃ = H, R₂ = (CH₂)₂COOH] (1.30 g) and triethylamine (1.15 mL) in THF (15 mL) at 0°C. After 5 minutes the solution was saturated with ammonia gas, then the mixture was stirred at 20°C for 16 hours. The 15 reaction was then quenched with water and extracted with EtOAc. Evaporation gave a solid, which was purified by chromatography on silica gel, eluting with EtOAc, to give 3-(3-indolyl)propanamide

20 [II: R₁ = R₃ = H, R₂ = (CH₂)₂CONH₂] (1.09 g, 84%); mp (MeOH/water) 134-136°C (Crosby DG, Boyd JB, Johnson HE, J. Org. Chem. 1960;25:1826 record mp 131.5-133°C).

25 ^1H NMR ((CD₃)₂CO): δ 9.95 (1H, s, NH), 7.58 (1H, dt, J = 8.2, 0.7 Hz, ArH), 7.36 (1H, dt, J = 8.1, 0.8 Hz, ArH), 7.13 (1H, m, H-2), 7.08 (1H, ddd, J = 8.1, 7.0, 1.1 Hz, ArH), 7.00 (1H, ddd, J = 8.0, 7.0, 1.0 Hz, ArH), 6.75, 6.12 (2xH, 2xbr s, CONH₂), 3.04 (2H, m, 3-CH₂), 2.05 (2H, m, 3-CH₂CH₂).

30 ^{13}C NMR: δ 174.87 (s, CONH₂), 137.75, 128.44 (2xs, Ar), 122.80, 122.02 (2xd, Ar), 119.30 (2xd, Ar), 115.67 (s, Ar), 112.08 (d, Ar), 37.05 (t, 3-CH₂CH₂), 21.87 (t, 3-CH₂).

The above amide (1.03 g) was treated with S₂Cl₂ as above, then the product mixture obtained after workup

-64-

was treated successively with NaBH_4 then H_2O_2 as described above. The resulting oil was chromatographed on silica gel, eluting with EtOAc:light petroleum (3:1), to give firstly 2,2'-thiobis[3-(3-indolyl)-propanamide] [VI: $n = 1$; $R_1 = R_3 = \text{H}$, $R_2 = (\text{CH}_2)_2\text{CONH}_2$] (0.16 g, 14%); mp (EtOAc/light petroleum) 196.5-197.5°C.

^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 11.02 (1H, s, NH), 7.55 (1H, d, $J = 8.0$ Hz, ArH), 7.38 (1H, s, NH), 7.26 (1H, d, $J = 8.1$ Hz, ArH), 7.08 (1H, ddd, $J = 8.0, 7.1, 0.8$ Hz, ArH), 6.98 (1H, dd, $J = 7.8, 7.1$ Hz, ArH), 6.85 (1H, s, NH), 3.16, 2.46 (2x2H, 2xt, $J = 7.7$ Hz, 3- CH_2CH_2).

^{13}C NMR: δ 174.26 (s, CONH_2), 136.77, 126.82, 123.29 (3xs, Ar), 122.09, 118.82, 118.68 (3xd, Ar), 118.43 (s, Ar), 111.12 (d, Ar), 35.94 (t, 3- CH_2CH_2), 20.58 (t, 3- CH_2).

Analysis calculated for $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$ requires:

C, 65.0; H, 5.4; N, 13.8; S, 7.9%.

Found: C, 64.8; H, 5.7; N, 13.6; S, 7.7%.

Further elution with EtOAc and EtOAc:EtOH (9:1) gave 2,2'-dithiobis[3-(3-indolyl)propanamide] (50) [VI: $n = 2$; $R_1 = R_3 = \text{H}$, $R_2 = (\text{CH}_2)_2\text{CONH}_2$] (0.90 g, 75%) as a yellow oil. A subsample crystallized from MeOH/dilute HCl as a solid which decomposed above 101°C.

^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 11.37 (1H, s, NH), 7.55 (1H, d, $J = 8.0$ Hz, ArH), 7.32 (1H, d, $J = 8.2$ Hz, ArH), 7.16 (1H, t, $J = 7.6$ Hz, ArH), 7.00 (1H, t, $J = 7.5$ Hz, ArH), 6.94, 6.64 (2x1H, 2xs, CONH_2), 2.72, 2.14 (2x2H, 2xm, 3- CH_2CH_2).

^{13}C NMR: δ 173.48 (s, CONH_2), 137.42, 126.58, 125.09 (3xs, Ar), 123.29 (d, Ar), 122.65 (s, Ar), 119.53, 118.91, 111.46 (3xd, Ar), 36.48 (t, 3- CH_2CH_2), 20.26 (t, 3- CH_2).

-65-

Analysis calculated for $C_{22}H_{22}N_4O_2S_2 \cdot 0.5H_2O$ requires:

C, 59.1; H, 5.2; N, 12.5; S, 14.3%.

Found: C, 59.1; H, 5.4; N, 12.2; S, 14.0%.

5 Reduction of (50) with $NaBH_4$ as above gave a quantitative yield of 3-(2-thioxo-3-indoliny)-propanamide (14) [IV: $R_1 = R_2 = H$, $R_3 = (CH_2)_2CONH_2$]; mp (EtOAc) 160-163°C.

1H NMR ($(CD_3)_2SO$): δ 12.63 (1H, s, NH), 7.38 (1H, d, $J = 7.3$ Hz, ArH), 7.27 (1H, t, $J = 7.6$ Hz, ArH), 7.22 (1H, s, NH), 7.12 (1H, t, $J = 7.5$ Hz, ArH), 7.00 (1H, d, $J = 7.7$ Hz, ArH), 6.70 (1H, s, NH), 3.84 (1H, t, $J = 5.4$ Hz, H-3), 2.38 (1H, m, 3- CH_2CH_2), 2.16-1.96 (2H, m, 3- CH_2CH_2), 1.77 (1H, ddd, $J = 14.6, 10.3, 4.2$ Hz, 3- CH_2CH_2).

15 ^{13}C NMR: δ 206.83 (s, CSNH), 173.37 ($CONH_2$), 144.11, 133.81 (2xs, Ar), 127.95, 124.11, 123.21, 110.03 (4xd, Ar), 56.35 (d, C-3), 30.12, 28.32 (2xt, 3- CH_2CH_2).

Analysis calculated for $C_{11}H_{12}N_2OS$ requires:

C, 60.0; H, 5.5; N, 12.7; S, 14.6%.

20 Found: C, 60.0; H, 5.5; N, 12.8; S, 14.3%.

Compound 51 of Table 1

DEPC (98%, 1.08 mL) was added to a stirred solution of 3-(3-indolyl)propanoic acid

25 [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2COOH$] (1.10 g), triethylamine (1.94 mL) and methylamine hydrochloride (0.47 g) in THF (20 mL) at 0°C, then the mixture was stirred at 20°C for 20 hours. The reaction was then quenched with water and extracted with EtOAc.

30 Evaporation gave an oil which was purified by chromatography on silica gel. Elution with EtOAc gave firstly foreruns, then *N*-methyl-3-(3-indolyl)-propanamide [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONHMe$] (0.81 g, 69%); mp (CH_2Cl_2 /light petroleum) 97.5-99°C

-66-

(Kononova VV, Vereshchagin AL, Polyachenka VM, Semenov AA, Khim.-Farm. Zh. 1978;12:30 record mp 97-99°C).

¹H NMR ((CD₃)₂CO): δ 9.97 (1H, s, NH), 7.56 (1H, dd, J = 8.0, 0.8 Hz, ArH), 7.36 (1H, dt, J = 8.1, 0.8 Hz, ArH), 7.11 (1H, m, H-2), 7.08 (1H, ddd, J = 8.1, 7.0, 1.1 Hz, ArH), 6.99 (1H, ddd, J = 7.8, 7.0, 1.0 Hz, ArH), 6.99 (1H, br s, NHCH₃), 3.04 (2H, td, J = 7.7, 0.9 Hz, 3-CH₂), 2.68 (3H, d, J = 4.7 Hz, NHCH₃), 2.51 (2H, t, J = 7.7 Hz, 3-CH₂CH₂).

¹³C NMR: δ 173.30 (s, CONH), 137.73, 128.42 (2xs, Ar), 122.80, 122.01, 119.31 (3xd, Ar), 115.62 (s, Ar), 112.08 (d, Ar), 37.67 (t, 3-CH₂CH₂), 26.06 (q, NCH₃), 22.08 (t, 3-CH₂).

The above N-methylpropanamide (0.75 g) was treated with S₂Cl₂ as above, then the product mixture obtained after workup was treated successively with NaBH₄ then H₂O₂ as described above. The resulting oil was chromatographed on silica gel, eluting with EtOAc, to give firstly 2,2'-thiobis[N-methyl-3-(3-indolyl)-propanamide] [VI: n = 1; R₁ = R₃ = H, R₂ = (CH₂)₂CONHMe] (0.13 g, 16%); mp (EtOAc/benzene/light petroleum) 120-123°C.

¹H NMR (CDCl₃): δ 10.50 (1H, s, NH), 7.54 (1H, d, J = 7.9 Hz, ArH), 7.31 (1H, d, J = 8.1 Hz, ArH), 7.14 (1H, ddd, J = 8.1, 7.1, 1.0 Hz, ArH), 7.04 (1H, ddd, J = 7.9, 7.0, 0.9 Hz, ArH), 5.31 (1H, br d, J = 4.9 Hz, NHCH₃), 3.47 (2H, m, 3-CH₂), 2.80 (2H, m, 3-CH₂CH₂), 2.60 (3H, d, J = 4.9 Hz, NHCH₃).

¹³C NMR: δ 174.25 (s, CONH), 137.17, 126.67, 125.39 (3xs, Ar), 122.51, 118.88, 118.58 (3xd, Ar), 117.62 (s, Ar), 111.43 (d, Ar), 36.01 (t, 3-CH₂CH₂), 26.27 (q, NCH₃), 21.02 (t, 3-CH₂).

-67-

Analysis calculated for $C_{24}H_{26}N_4O_2S \cdot C_6H_6$ requires:

C, 70.3; H, 6.3; N, 10.9; S, 6.3%.

Found: C, 70.1; H, 6.2; N, 11.0; S, 6.0%.

Further elution with EtOAc gave

5 2,2'-dithiobis[N-methyl-3-(3-indolyl)propanamide] (51)
[V: $n = 2$; $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONHMe$] (0.29 g,
34%); mp (EtOAc/benzene/light petroleum) 162.5-164°C.
 1H NMR (CD_3CD): δ 7.50 (1H, dt, $J = 8.1$, 0.8 Hz, ArH),
7.33 (1H, dt, $J = 8.2$, 0.8 Hz, ArH), 7.18 (1H, ddd,
10 $J = 8.1$, 7.0, 1.0 Hz, ArH), 7.02 (1H, ddd, $J = 8.0$,
7.1, 0.8 Hz, ArH), 2.71 (2H, m, 3- CH_2), 2.49 (3H, s,
NCH₃), 2.02 (2H, m, 3- CH_2CH_2).
 ^{13}C NMR: δ 175.76 (s, CONH), 139.27, 128.33, 127.01
(3xs, Ar), 124.80, (d, Ar), 123.92 (s, Ar), 120.48,
15 120.44, 112.48 (3xd, Ar), 38.44 (t, 3- CH_2CH_2), 26.32
(q, NCH₃), 21.95 (t, 3- CH_2).

Analysis calculated for $C_{24}H_{26}N_4O_2S_2$ requires:

C, 61.8; H, 5.6; N, 12.0; S, 13.7%.

Found: C, 61.7; H, 5.7; N, 12.2; S, 13.7%.

20

Compound 52 of Table 1

A solution of 3-(3-indolyl)propanoic acid [II:
 $R_1 = R_3 = H$, $R_2 = (CH_2)_2COOH$] (0.70 g), triethylamine
(5 mL) and methoxyamine hydrochloride (0.90 g) in THF
25 (20 mL) was stirred at 20°C for 3 hours, then cooled to
0°C. DEPC (98%, 0.70 mL) was added, then the mixture
was stirred at 20°C for 18 hours. The reaction was
then quenched with water and extracted with EtOAc.
Evaporation gave an oil which was purified by
30 chromatography on silica gel. Elution with EtOAc:light
petroleum (1:1) gave foreruns, then elution with
EtOAc:light petroleum (3:1) gave N-methoxy-
3-(3-indolyl)propanamide [II: $R_1 = R_3 = H$,
 $R_2 = (CH_2)_2CONHOMe$] (0.50 g, 62%); mp (CH_2Cl_2 /light

-68-

petroleum) 116-118°C (Kononova VV, Vereshchagin AL, Polyachenka VM, Semenov AA, Khim.-Farm. Zh. 1978;12:30 record mp 114-115°C).

¹H NMR ((CD₃)₂SO): δ 10.97, 10.77 (2x1H, 2xs, 2xNH),
5 7.51 (1H, d, J = 7.8 Hz, ArH), 7.32 (1H, d, J = 8.1 Hz, ArH), 7.09 (1H, s, H-2), 7.06 (1H, td, J = 8.0, 1.0 Hz, ArH), 6.97 (1H, td, J = 8.0, 0.9 Hz, ArH), 3.55 (3H, s, NHOCH₃), 2.91, 2.30 (2x2H, 2xt, J = 7.6 Hz, 3-CH₂CH₂).
¹³C NMR: δ 168.72 (s, CONH), 136.13, 126.87 (2xs, Ar),
10 122.14, 120.83, 118.21, 118.09 (4xd, Ar), 113.30 (s, Ar), 111.23 (d, Ar), 63.00 (q, OCH₃), 33.20 (t, 3-CH₂CH₂), 20.53 (t, 3-CH₂).

The above N-methoxypropanamide (1.00 g) was treated with S₂Cl₂ as above, then the product mixture
15 obtained after workup was treated successively with NaBH₄ then H₂O₂ as described above. The resulting oil was chromatographed on silica gel, eluting with EtOAc:light petroleum (3:2), to give firstly 2,2'-thiobis[N-methoxy-3-(3-indolyl)propanamide]
20 [VI: n = 1; R₁ = R₃ = H, R₂ = (CH₂)₂CONHOMe] (0.12 g, 11%); mp (EtOAc/light petroleum) 157.5-158.5°C.
¹H NMR ((CD₃)₂SO): δ 11.02, 10.95 (2x1H, 2xs, 2xNH),
7.53 (1H, d, J = 7.9 Hz, ArH), 7.25 (1H, d, J = 8.1 Hz, ArH), 7.09 (1H, t, J = 7.5 Hz, ArH), 6.99 (1H, t,
25 J = 7.4 Hz, ArH), 3.52 (3H, s, NHOCH₃), 3.17, 2.31 (2x2H, 2xt, J = 7.5 Hz, 3-CH₂CH₂).
¹³C NMR: δ 168.73 (s, CONH), 136.75, 126.79, 123.29 (3xs, Ar), 122.23 (d, Ar), 118.78 (d, 2C, Ar), 118.00 (s, Ar), 111.08 (d, Ar), 63.04 (q, OCH₃), 33.43 (t, 3-CH₂CH₂), 20.46 (t, 3-CH₂).
30

Analysis calculated for C₂₄H₂₆N₄O₄S requires:

C, 61.8; H, 5.6; N, 12.0; S, 6.9%.

Found: C, 61.6; H, 5.8; N, 12.2; S, 6.9%.

-69-

Elution with EtOAc gave 2,2'-dithiobis[N-methoxy-3-(3-indolyl)propanamide] (52) [VI: $n = 2$; $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONHOMe$] (0.35 g, 31%); mp (EtOAc/light petroleum) 176-178°C.

5 1H NMR ($(CD_3)_2SO$): δ 11.39, 10.73 (2x1H, 2xs, 2xNH), 7.51 (1H, d, $J = 8.0$ Hz, ArH), 7.32 (1H, d, $J = 8.2$ Hz, ArH), 7.16 (1H, t, $J = 7.7$ Hz, ArH), 7.00 (1H, t, $J = 7.5$ Hz, ArH), 3.41 (3H, s, $NHOCH_3$), 2.65, 2.01 (2x2H, 2xt, $J = 7.4$ Hz, 3- CH_2CH_2).

10 ^{13}C NMR: δ 168.21 (s, CONH), 137.42, 126.52, 125.16 (3xs, Ar), 123.37 (d, Ar), 122.20 (s, Ar), 119.48, 118.96, 111.48 (3xd, Ar), 62.91 (q, OCH_3), 33.79 (t, 3- CH_2CH_2), 20.09 (t, 3- CH_2).

Analysis calculated for $C_{24}H_{26}N_4O_4S_2$ requires:

15 C, 57.8; H, 5.2; N, 11.2; S, 12.9%.

Found: C, 57.6; H, 5.4; N, 11.3; S, 12.7%.

Compound 53 of Table 1

DEPC (98%, 1.28 mL) was added to a stirred solution of 3-(3-indolyl)propanoic acid [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2COOH$] (1.04 g) and triethylamine (1.15 mL) in THF (15 mL) at 0°C. After 5 minutes the solution was saturated with dimethylamine gas, then the mixture was stirred at 20°C for 16 hours.

25 Workup as above and chromatography on silica gel, eluting with EtOAc, gave N,N-dimethyl

3-(3-indolyl)propanamide [II: $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONMe_2$] (0.90 g, 76%); mp (CH_2Cl_2 /light petroleum) 141-142°C (Avramenko VG, Suvorov NN, Mashkovskii MD, Mushulov PI, Eryshev BYa, Fedorova VS, Orlova IA, Trubitsyna TK, Khim.-Farm. Zh. 1970;4:10 record mp 139-140.5°C).

30 1H NMR (CD_3OD): δ 7.53 (1H, dt, $J = 7.9$, 0.9 Hz, ArH), 7.32 (1H, dt, $J = 8.1$, 0.8 Hz, ArH) 7.07 (1H, ddd,

-70-

$J = 8.1, 7.0, 1.1$ Hz, ArH), 7.04 (s, H-2), 6.99 (1H, ddd, $J = 7.9, 7.0, 0.9$ Hz, ArH), 3.05 (2H, m, 3-CH₂), 2.88, 2.86 (2x3H, 2xs, N(CH₃)₂), 2.73 (2H, m, 3-CH₂CH₂).
¹³C NMR: δ 175.75 (s, CON(CH₃)₂), 138.20, 128.59 (2xs, Ar), 123.11, 122.36, 119.61, 119.24 (4xd, Ar), 115.16 (s, Ar), 112.26 (d, Ar), 37.89, 35.82 (2xq, N(CH₃)₂), 35.30 (t, 3-CH₂CH₂), 22.32 (t, 3-CH₂).

The above dimethylpropanamide (0.82 g) was treated with S₂Cl₂ as above, then the product mixture obtained after workup was treated successively with NaBH₄ then H₂O₂ as described above. The resulting oil was chromatographed on silica gel, eluting with EtOAc:light petroleum (3:2), to give firstly 2,2'-thiobis-[N,N-dimethyl-3-(3-indolyl)propanamide] [VI: $n = 1$; R₁ = R₃ = H, R₂ = (CH₂)₂CONHMe₂] (0.12 g, 14%); mp (EtOAc/light petroleum) 189-190°C.

¹H NMR (CDCl₃): δ 10.72 (br s, 1 H, NH), 7.55 (1H, d, $J = 7.9$ Hz, ArH), 7.24 (1H, d, $J = 8.1$ Hz, ArH), 7.10 (ddd, $J = 8.0, 7.1, 0.9$ Hz, 1 H, ArH), 7.02 (dd, $J = 7.9, 7.1$ Hz, 1 H, ArH), 3.47, 2.97 (2x2H, 2xm, 3-CH₂CH₂), 2.95, 2.91 (2x3H, 2xs, N(CH₃)₂).
¹³C NMR: δ 173.36 (s, CON(CH₃)₂), 137.15, 126.92, 125.55 (3xs, Ar), 122.26, 118.68, 118.58 (3xd, Ar), 118.02 (s, Ar), 111.35 (d, Ar), 37.49, 35.74 (2xq, N(CH₃)₂), 32.14 (t, 3-CH₂CH₂), 20.54 (t, 3-CH₂).

Analysis calculated for C₂₆H₃₀N₄O₂S requires:

C, 67.5; H, 6.5; N, 12.1; S, 6.9%.

Found: C, 67.4; H, 6.6; N, 12.0; S, 7.2%.

Elution with EtOAc gave 2,2'-dithiobis-[N,N-dimethyl-3-(3-indolyl)propanamide] (53) [VI: $n = 2$; R₁ = R₃ = H, R₂ = (CH₂)₂CONMe₂] (0.49 g, 52%); mp (EtOAc) 179-180°C.

¹H NMR (CD₃OD): δ 7.45 (1H, dt, $J = 8.0, 0.8$ Hz, ArH), 7.32 (1H, dt, $J = 8.2, 0.8$ Hz, ArH), 7.17 (1H, ddd,

-71-

$J = 8.2, 7.1, 1.1$ Hz, ArH), 7.01 (1H, ddd, $J = 8.0, 7.1, 0.9$ Hz, ArH), 2.72 (2H, m, 3-CH₂CH₂), 2.71, 2.44 (2x3H, 2xs, N(CH₃)₂), 2.09 (2H, m, 3-CH₂CH₂).

¹³C NMR: δ 174.68 (s, CON(CH₃)₂), 139.43, 128.26, 126.61 (3xs, Ar), 124.85 (d, Ar), 123.84 (s, Ar), 120.55, 120.28, 112.51 (3xd, Ar), 37.57 (q, NCH₃), 35.69 (t, 3-CH₂CH₂), 35.60 (q, NCH₃), 21.49 (t, 3-CH₂).

Analysis calculated for C₂₆H₃₀N₄O₂S₂ requires:

C, 63.2; H, 6.1; N, 11.3; S, 13.0%.

Found: C, 63.2; H, 6.2; N, 11.3; S, 13.1%.

Compound 54 of Table 1

DEPC (98%, 0.69 mL) was added to a stirred solution of 3-(3-indolyl)propanoic acid

[II: R₁ = R₃ = H, R₂ = (CH₂)₂COOH] (0.70 g) and phenethylamine (1.1 mL) in THF (15 mL) at 0°C, then the mixture was stirred at 20°C for 3 hours. Workup and chromatography on silica gel, eluting with EtOAc/light petroleum (1:1) gave *N*-(2-phenylethyl)-3-(3-indolyl)-propanamide [II: R₁ = R₃ = H, R₂ = (CH₂)₂CONH(CH₂)₂Ph] (0.58 g, 54%); mp (EtOAc/light petroleum) 88-89°C.

¹H NMR (CDCl₃): δ 8.02 (1H, br s, NH), 7.58 (1H, d, $J = 7.9$ Hz, ArH), 7.36 (1H, d, $J = 8.1$ Hz, ArH), 7.24-7.15 (4H, m, ArH), 7.12 (1H, ddd, $J = 7.9, 7.0, 0.8$ Hz, ArH), 6.99 (2H, dd, $J = 7.4, 1.7$ Hz, ArH), 6.95 (1H, d, $J = 2.2$ Hz, H-2), 5.34 (1H, br t, $J = 6.0$ Hz, NHCH₂), 3.44 (2H, q, $J = 6.6$ Hz, NHCH₂), 3.09 (2H, t, $J = 7.3$ Hz, 3-CH₂), 2.66 (2H, t, $J = 6.9$ Hz, NHCH₂CH₂), 2.52 (2H, t, $J = 7.3$ Hz, 3-CHCH₂).

¹³C NMR: δ 172.64 (s, CONH), 138.90, 136.38 (2xs, Ar), 128.71, 128.58 (2xd, 2x2C, Ar), 127.13 (s, Ar), 126.41, 122.10, 121.77, 119.37, 118.72 (5xd, Ar), 114.95 (s, Ar), 111.23 (d, Ar), 40.48, 37.42, 35.62 (3xt, 3-CH₂CH₂CONH(CH₂)₂), 21.35 (t, 3-CH₂).

-72-

Analysis calculated for $C_{19}H_{20}N_2O$ requires:

C, 78.1; H, 6.9; N, 9.6%.

Found: C, 77.9; H, 7.0; N, 9.6%.

The above phenylethylpropanamide (0.53 g) was
5 treated with S_2Cl_2 as above, then the product mixture
obtained after workup was treated successively with
 $NaBH_4$ then H_2O_2 as described above. The resulting oil
was chromatographed on silica gel, eluting with
EtOAc:light petroleum (1:2), to give firstly
10 2,2'-thiobis[N-(2-phenylethyl)-3-(3-indolyl)-
propanamide] [VI: $n = 1$; $R_1 = R_3 = H$,
 $R_2 = (CH_2)_2CONH(CH_2)_2Ph$] (0.13 g, 23%); mp (EtOAc/light
petroleum) 120-121.5°C.

1H NMR ($CDCl_3$): δ 10.69 (1H, s, NH), 7.55 (1H, d,
15 $J = 7.9$ Hz, ArH), 7.35 (1H, d, $J = 8.2$ Hz, ArH), 7.17
(1H, ddd, $J = 8.1, 7.1, 1.0$ Hz, ArH), 7.08 (1H, ddd,
 $J = 8.0, 0.9$ Hz, ArH), 7.02 (1H, t, $J = 7.4$ Hz, ArH),
6.93 (2H, t, $J = 7.4$ Hz, ArH), 6.33 (2H, d, $J = 7.2$ Hz,
ArH), 5.26 (1H, t, $J = 5.9$ Hz, $NHCH_2$), 3.51 (2H, m,
20 3- CH_2), 3.14 (2H, q, $J = 6.6$ Hz, $NHCH_2$), 2.77 (2H, m,
3- CH_2CH_2), 1.92 (2H, t, $J = 6.8$ Hz, $NHCH_2CH_2$).
 ^{13}C NMR: δ 173.62 (s, CONH), 138.20, 137.33 (2xs, Ar),
128.40, 128.36 (2xd, 2x2C, Ar), 126.76 (s, Ar), 126.16
(d, Ar), 125.51 (s, Ar), 122.78, 119.17, 118.70 (3xd,
25 Ar), 117.57 (s, Ar), 111.70 (d, Ar), 40.49, 36.43,
35.46 (3xt, 3- $CH_2CH_2CONH(CH_2)_2$), 21.35 (t, 3- CH_2).

Analysis calculated for $C_{38}H_{38}N_4O_2S$ requires:

C, 74.2; H, 6.2; N, 9.1; S, 5.2%.

Found: C, 74.4; H, 6.4; N, 9.0; S, 5.2%.

30 Elution with EtOAc:light petroleum (2:3)
gave 2,2'-dithiobis[N-(2-phenylethyl)-3-(3-indolyl)-
propanamide] (54) [VI: $n = 2$; $R_1 = R_3 = H$,
 $R_2 = (CH_2)_2CONH(CH_2)_2Ph$] (0.36 g, 61%) as an oil.

-73-

¹H NMR (CDCl₃): δ 8.42 (1H, s, NH), 7.51 (1H, d, J = 8.0 Hz, ArH), 7.32-7.16 (5H, m, ArH), 7.04 (3H, m, ArH), 4.63 (1H, t, J = 5.9 Hz, NHCH₂), 3.23 (2H, q, J = 6.7 Hz, NHCH₂), 2.85 (t, J = 7.8 Hz, 3-CH₂), 2.59 (2H, t, J = 7.0 Hz, NHCH₂CH₂), 1.81 (2H, t, J = 7.8 Hz, 3-CH₂CH₂).

¹³C NMR: δ 171.95 (s, CONH), 139.15, 137.23 (2xs, Ar), 128.87, 128.55 (2xd, 2x2C, Ar), 127.02 (s, Ar), 126.39 (d, Ar), 125.50 (s, Ar), 124.33 (d, Ar), 123.98 (s, Ar), 120.11, 119.88, 111.17 (3xd, Ar), 40.62, 37.37, 35.58 (3xt, 3-CH₂H₂CONH(CH₂)₂), 20.64 (t, 3-CH₂).

HRFABMS m/z calculated for C₃₈H₃₉N₄O₂S₂:

647.2514 (MH⁺)

Found: 647.2471.

Compounds 55 and 56 of Table 1

A solution of 3-(3-indolyl)propanoic acid [II: R₁ = R₃ = H, R₂ = (CH₂)₂COOH] (0.80 g), triethylamine (10 mL) and methyl 4-(aminomethyl)benzoate hydrochloride (Nair MG, Baugh CM, J. Org. Chem. 1973;38:2185) (1.29 g) in THF (20 mL) was stirred at 20°C for 15 minutes, then cooled to 0°C. DEPC (98%, 1.00 mL) was added, then the mixture was stirred at 20°C for 18 hours. Workup and chromatography on silica gel, eluting with EtOAc:light petroleum (5:3) gave N-(4-methoxycarbonylbenzyl)-3-(3-indolyl)propanamide [II: R₁ = R₃ = H, R₂ = (CH₂)₂CONHCH₂Ph{4-COOMe}] (1.10 g, 77%); mp (CH₂Cl₂/light petroleum) 130-132°C. ¹H NMR (CDCl₃): δ 8.08 (1H, s, NH), 7.88 (2H, d, J = 8.2 Hz, ArH), 7.60 (1H, d, J = 7.8 Hz, ArH), 7.36 (1H, d, J = 8.1 Hz, ArH), 7.19 (1H, ddd, J = 8.1, 7.1, 0.9 Hz, ArH), 7.11 (1H, ddd, J = 7.9, 7.2, 0.7 Hz, ArH), 7.06 (2H, d, J = 8.2 Hz, ArH), 6.94 (1H, d, J = 2.3 Hz, H-2), 5.74 (1H, br t, J = 5.9 Hz, NHCH₂),

-74-

4.38 (2H, d, $J = 5.9$ Hz, NHCH_2), 3.90 (3H, s, OCH_3),
3.15, 2.63 (2x2H, 2xt, $J = 7.2$ Hz, 3- CH_2CH_2).
 ^{13}C NMR: δ 172.68 (s, CONH), 166.87 (s, COOCH_3),
143.50, 136.37 (2xs, Ar), 129.80 (2xd, Ar), 129.10 (s,
5 Ar), 127.28 (2xd, Ar), 127.03 (s, Ar), 122.11, 121.92,
119.41, 118.64 (4xd, Ar), 114.66 (s, Ar), 111.27 (d,
Ar), 52.09 (q, OCH_3), 43.05 (t, NHCH_2), 37.37 (t,
3- CH_2CH_2), 21.39 (t, 3- CH_2).

Analysis calculated for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$ requires:

10 C, 71.4; H, 6.0; N, 8.3%.

Found: C, 71.1; H, 5.7; N, 8.4%.

The above methoxycarbonylbenzylpropanamide
(1.08 g) was treated with S_2Cl_2 as above, then the
product mixture obtained after workup was treated
15 successively with NaBH_4 then H_2O_2 as described above.
The resulting oil was chromatographed on silica gel,
eluting with EtOAc:light petroleum (2:3), to give
firstly 2,2'-thiobis[N-(4-methoxycarbonylbenzyl)-
3-(3-indolyl)propanamide] [VI: $n = 1$; $\text{R}_1 = \text{R}_3 = \text{H}$,
20 $\text{R}_2 = (\text{CH}_2)_2\text{CONHCH}_2\text{Ph}\{4\text{-COOMe}\}$] (0.18 g, 16%);
mp (MeOH/dilute HCl) 101-104.5°C (dec).

^1H NMR (CDCl_3): δ 10.28 (1H, s, NH), 7.47 (1H, d,
 $J = 7.7$ Hz, ArH), 7.45 (2H, d, $J = 8.4$ Hz, ArH), 7.05
(1H, d, $J = 8.0$ Hz, ArH), 6.97 (1H, ddd, $J = 8.0$, 6.9,
25 1.1 Hz, ArH), 6.91 (1H, ddd, $J = 7.9$, 6.8, 1.1 Hz,
ArH), 6.61 (2H, d, $J = 8.3$ Hz, ArH), 6.34 (1H, br t,
 $J = 5.8$ Hz, NHCH_2), 4.40 (2H, d, $J = 5.9$ Hz, NHCH_2),
3.79 (3H, s, OCH_3) 3.54, 2.97 (2x2H, 2xm, 3- CH_2CH_2).

^{13}C NMR: δ 174.37 (s, CONH), 166.75 (s, COOCH_3),
30 142.31, 137.15 (2xs, Ar), 129.35 (d, 2C, Ar), 128.39,
126.52 (2xs, Ar), 126.24 (d, 2C, Ar), 125.30 (s, Ar),
122.65, 118.87, 118.49 (3xd, Ar), 117.92 (s, Ar),
111.31 (d, Ar), 51.95 (q, OCH_3), 43.22 (t, NHCH_2),
36.34 (t, 3- CH_2CH_2), 21.17 (t, 3- CH_2).

-75-

Analysis calculated for $C_{40}H_{38}N_4O_6S \cdot 0.5H_2O$ requires:

C, 67.5; H, 5.5; N, 7.9%.

Found: C, 67.4; H, 5.4; N, 8.1%.

Elution with EtOAc:light petroleum (1:1) gave

- 5 2,2'-dithiobis[N-(4-methoxycarbonylbenzyl)-3-(3-indolyl)propanamide] (55) [VI: $n = 2$; $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONHCH_2Ph\{4-COOMe\}$] (0.50 g, 42%);
mp (EtOAc/light petroleum) 151-153°C.
 1H NMR ($(CD_3)_2SO$): δ 11.42 (1H, s, NH), 8.06 (1H, t, $J = 5.7$ Hz, $NHCH_2$), 7.81 (2H, d, $J = 8.2$ Hz, ArH), 7.55 (1H, d, $J = 8.0$ Hz, ArH), 7.34 (1H, d, $J = 8.2$ Hz, ArH), 7.17 (1H, t, $J = 7.6$ Hz, ArH), 7.11 (2H, d, $J = 8.1$ Hz, ArH), 6.99 (1H, t, $J = 7.5$ Hz, ArH), 4.19 (2H, d, $J = 5.8$ Hz, $NHCH_2$), 3.84 (3H, s, OCH_3), 2.73, 2.24 (2x2H, 2xt, $J = 7.5$ Hz, 3- CH_2CH_2).
10 ^{13}C NMR: δ 171.48 (s, CONH), 166.00 (s, $COOCH_3$), 145.01, 137.37 (2xs, Ar), 128.98 (d, 2C, Ar), 127.84 (s, Ar), 127.01 (d, 2C, Ar), 126.53, 125.21 (2xs, Ar), 123.24 (d, Ar), 122.39 (s, Ar), 119.57, 118.86, 111.38 (3xd, Ar), 51.93 (q, OCH_3), 41.62 (t, $NHCH_2$), 36.65 (t, 3- CH_2CH_2), 20.38 (t, 3- CH_2).
15

Analysis calculated for $C_{40}H_{38}N_4O_6S_2$ requires:

C, 65.4; H, 5.2; N, 7.6; S, 8.7%.

Found: C, 65.5; H, 5.5; N, 7.3; S, 8.8%.

- 25 Hydrolysis of 55 (0.24 g) with K_2CO_3 in MeOH/water at 30°C for 1 day, then 50°C for 1 hour, under nitrogen as above gave an oil. Chromatography on silica gel, eluting with EtOAc:light petroleum (1:1) containing 1% AcOH, gave 2,2'-dithiobis[N-(4-carboxybenzyl)-3-(3-indolyl)propanamide] (56) [VI: $n = 2$; $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONHCH_2Ph\{4-COOH\}$] (60 mg, 26%);
mp (MeOH/dilute HCl) 135.5-138.5°C (decomposed).
30 1H NMR ($(CD_3)_2SO$): δ 11.41 (1H, s, NH), 8.03 (1H, t, $J = 5.8$ Hz, $NHCH_2$), 7.79 (2H, d, $J = 8.2$ Hz, ArH), 7.55

-76-

(1H, d, $J = 8.0$ Hz, ArH), 7.33 (1H, d, $J = 8.2$ Hz, ArH), 7.16 (1H, t, $J = 7.6$ Hz, ArH), 7.09 (2H, d, $J = 8.1$ Hz, ArH), 6.99 (1H, t, $J = 7.5$ Hz, ArH), 4.18 (2H, d, $J = 5.8$ Hz, NHCH_2), 2.73, 2.23 (2x2H, 2xt, $J = 7.5$ Hz, 3- CH_2CH_2).

^{13}C NMR: δ 171.44 (s, CONH), 167.10 (s, COOH), 144.46, 137.37 (2xs, Ar), 129.14 (d, 2C, Ar), 129.05 (s, Ar), 126.87 (d, 2C, Ar), 126.53, 125.18 (2xs, Ar), 123.23 (d, Ar), 122.40 (s, Ar), 119.58, 118.85, 111.37 (3xd, Ar), 41.65 (t, NHCH_2), 36.42 (t, 3- CHCH_2), 20.37 (t, 3- CH_2).

Analysis calculated for $\text{C}_{38}\text{H}_{34}\text{N}_4\text{O}_6\text{S}_2 \cdot \text{H}_2\text{O}$ requires:

C, 63.0; H, 5.0; N, 7.7; S, 8.8%.

Found: C, 62.5; H, 5.2; N, 8.2; S, 8.8%.

Compounds 57 and 58 of Table 1

A stirred solution of methyl 2-acetoxy-4-bromomethylbenzoate (Regnier G, Canevari R, Le Douarec J-C, Bull. Soc. Chim. Fr. 1966:2821) (10.7 g) and hexamethylenetetramine (17.1 g) in CHCl_3 (150 mL) was refluxed for 5 hours, then the solvent was removed (method of Meindl W, v Angerer E, Ruckdeschel G, Schonenberger H, Arch. Pharm. (Weinheim) 1982;315:941). The residue was stirred with MeOH (60 mL) and concentrated HCl (30 mL) at 20°C for 10 minutes, then the solvent removed. Treatment of the solid residue twice more with HCl/MeOH and evaporation gave a solid, which was washed with CH_2Cl_2 , then treated with saturated KHCO_3 solution. The base was extracted with EtOAc and CH_2Cl_2 , then the solvents removed. The crude hydrochloride salt (5.30 g, 70% pure) was precipitated from an ethereal solution of the base upon the addition of HCl gas. A subsample of the

- 77 -

above crude base was purified by chromatography on silica gel, eluting with EtOAc/light petroleum (1:2). Acidification of a solution of the purified base gave pure methyl 4-(aminomethyl)-2-hydroxybenzoate

5 hydrochloride; mp (CH_2Cl_2 /light petroleum) 225-227°C.

^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 10.56 (1H, s, OH), 8.58 (3H, br s, NH_3^+), 7.78 (1H, d, $J = 8.1$ Hz, H-6), 7.14 (1H, s, H-3), 7.05 (1H, d, $J = 8.1$ Hz, H-5), 4.01 (2H, br s, 4- CH_2), 3.88 (3H, s, OCH_3).

10 ^{13}C NMR: δ 168.81 (s, COOCH_3), 159.80 (s, C-2), 141.84 (s, C-4), 130.25 (d, C-6), 119.61 (d, C-5), 117.48 (d, C-3), 112.90 (s, C-1), 52.53 (q, OCH_3), 41.63 (t, 4- CH_2).

Analysis calculated for $\text{C}_9\text{H}_{11}\text{NO}_3 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$ requires:

15 C, 47.7; H, 5.8; N, 6.2; Cl, 15.7%.

Found: C, 47.9; H, 5.8; N, 6.3; Cl, 15.9%.

A solution of 3-(3-indolyl)propanoic acid [II:

$\text{R}_1 = \text{R}_3 = \text{H}$, $\text{R}_2 = (\text{CH}_2)_2\text{COOH}$] (1.50 g), triethylamine (10 mL) and crude methyl 4-(aminomethyl)-

20 2-hydroxybenzoate hydrochloride (3.46 g) in DMF (20 mL) was stirred at 20°C for 10 minutes, then cooled to 0°C. DEPC (98%, 1.47 mL) was added, then the mixture was stirred at 20°C for 17 hours. Workup and

25 chromatography on silica gel, eluting with EtOAc:light petroleum (1:1) gave N-(3-hydroxy-4-methoxycarbonyl-benzyl)-3-(3-indolyl)propanamide [II: $\text{R}_1 = \text{R}_3 = \text{H}$, $\text{R}_2 = (\text{CH}_2)_2\text{CONHCH}_2\text{Ph}\{3\text{-OH}, 4\text{-COOMe}\}$] (1.40 g, 50%); mp (EtOAc/light petroleum) 132-133°C.

30 ^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 10.76 (1H, br s, NH), 10.50 (1H, s, OH), 8.41 (1H, t, $J = 5.8$ Hz, NHCH_2), 7.70 (1H, d, $J = 8.1$ Hz, ArH), 7.54 (1H, d, $J = 7.8$ Hz, ArH), 7.33 (1H, d, $J = 8.1$ Hz, ArH), 7.10 (1H, d, $J = 2.2$ Hz, H-2), 7.06 (1H, ddd, $J = 8.0, 7.1, 0.9$ Hz, ArH), 6.97 (1H, ddd, $J = 7.8, 7.0, 0.8$ Hz, ArH), 6.83 (1H, d,

-78-

$J = 1.4$ Hz, ArH), 6.74 (1H, dd, $J = 8.2, 1.4$ Hz, ArH), 4.27 (2H, d, $J = 6.0$ Hz, NHCH_2), 3.88 (3H, s, OCH_3), 2.96, 2.54 (2x2H, 2xt, $J = 7.7$ Hz, 3- CH_2CH_2).

^{13}C NMR: δ 172.05 (s, CONH), 169.14 (s, COOCH_3), 160.10, 148.27, 136.22 (3xs, Ar), 129.92 (d, Ar), 126.98 (s, Ar), 122.14, 120.84, 118.30, 118.12, 118.09, 115.41 (6xd, Ar), 113.68 (s, Ar), 111.27 (d, Ar), 111.20 (s, Ar), 52.34 (q, OCH_3), 41.67 (t, NHCH_2), 36.23 (t, 3- CH_2CH_2), 21.00 (t, 3- CH_2).

Analysis calculated for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4$ requires:

C, 68.2; H, 5.7; N, 8.0%.

Found: C, 68.3; H, 5.9; N, 8.0%.

A solution of acetyl chloride (0.42 mL) in THF (5 mL) was added to a stirred solution of the above propanamide (1.22 g) and triethylamine (1.00 mL) in THF (15 mL) at 0°C , then the mixture was stirred at 20°C for 18 hours. The reaction was then quenched with water (100 mL) and extracted with EtOAc (3 x 100 mL). Evaporation and chromatography on silica gel, eluting with EtOAc:light petroleum (2:1) gave *N*-(3-acetoxy-4-methoxycarbonylbenzyl)-3-(3-indolyl)propanamide [II: $\text{R}_1 = \text{R}_3 = \text{H}$, $\text{R}_2 = (\text{CH}_2)_2\text{CONHCH}_2\text{Ph}\{3\text{-OAc}, 4\text{-COOMe}\}$] (1.28 g, 94%) as an oil.

^1H NMR (CDCl_3): δ 8.18 (1H, br s, NH), 7.87 (1H, d, $J = 8.1$ Hz, ArH), 7.57 (1H, d, $J = 8.0$ Hz, ArH), 7.31 (1H, dt, $J = 8.1, 0.8$ Hz, ArH), 7.17 (1H, ddd, $J = 8.1, 7.0, 1.1$ Hz, ArH), 7.09 (1H, ddd, $J = 7.9, 7.0, 0.9$ Hz, ArH), 6.97 (1H, dd, $J = 8.1, 1.6$ Hz, ArH), 6.84 (1H, d, $J = 1.5$ Hz, ArH), 6.77 (1H, d, $J = 2.3$ Hz, H-2), 5.67 (1H, br t, $J = 5.8$ Hz, NHCH_2), 4.31 (2H, d, $J = 6.0$ Hz, NHCH_2), 3.87 (3H, s, COOCH_3), 3.11, 2.58 (2x2H, 2xt, $J = 6.9$ Hz, 3- CH_2CH_2), 2.36 (3H, s, OCOCH_3).

^{13}C NMR: δ 172.84 (s, CONH), 170.14 (s, OCOCH_3), 164.64 (s, COOCH_3), 150.82, 145.26, 136.33 (3xs, Ar),

-79-

132.04 (d, Ar), 126.85 (s, Ar), 125.42, 122.93, 122.31, 121.95 (4xd, Ar), 121.87 (s, Ar), 119.28, 118.52 (2xd, Ar), 114.08 (s, Ar), 111.36 (d, Ar), 52.23 (q, OCH₃), 42.62 (t, NHCH₂), 37.32 (t, 3-CH₂CH₂), 21.46 (t, 3-CH₂), 21.06 (q, OCOCH₃).

HREIMS *m/z* calculated for C₂₂H₂₂N₂O₅:

394.1529 (M⁺).

Found: 394.1526.

The above O-acetate (1.47 g) was treated with S₂Cl₂ as above, then the product mixture obtained after workup was treated successively with NaBH₄ then H₂O₂ as described above. Hydrolysis of the resulting oil with excess KHCO₃ in MeOH/water at 20°C for 1 hour (to remove the acetate group) gave an oil which was purified by chromatography on silica gel. Elution with EtOAc:light petroleum (1:2) gave firstly 2,2'-thiobis[N-(3-hydroxy-4-methoxycarbonylbenzyl)-3-(3-indolyl)propanamide] [VI: n = 1; R₁ = R₃ = H, R₂ = (CH₂)₂CONHCH₂Ph{3-OAc, 4-COOMe}] (0.12 g, 9%); mp (MeOH/dilute HCl) 109-112°C (decomposed). ¹H NMR (CDCl₃): δ 10.50 (1H, s, OH), 10.17 (1H, s, NH), 7.49 (1H, d, J = 7.9 Hz, ArH), 7.31 (1H, d, J = 8.2 Hz, ArH), 7.19 (1H, d, J = 8.1 Hz, ArH), 7.07 (1H, ddd, J = 8.0, 7.1, 0.8 Hz, ArH), 6.97 (1H, ddd, J = 7.8, 7.2, 0.6 Hz, ArH), 6.32 (1H, d, J = 1.1 Hz, ArH), 5.98 (1H, dd, J = 8.2, 1.5 Hz, ArH), 5.72 (1H, t, J = 5.7 Hz, NHCH₂), 4.22 (2H, d, J = 5.7 Hz, NHCH₂), 3.86 (3H, s, OCH₃), 3.50, 2.88 (2x2H, 2xm, 3-CH₂CH₂). ¹³C NMR: δ 173.77 (s, CONH), 170.06 (s, COOCH₃), 161.36, 145.57, 137.16 (3xs, Ar), 130.02 (d, Ar), 126.62, 125.16 (2xs, Ar), 122.69, 119.13, 118.43 (3xd, Ar), 117.65 (s, Ar), 117.40, 115.51, 111.53 (3xd, Ar), 111.07 (s, Ar), 52.18 (q, OCH₃), 43.19 (t, NHCH₂), 36.32 (t, 3-CH₂CH₂), 21.22 (t, 3-CH₂).

-80-

Analysis calculated for $C_{40}H_{38}N_4O_8S$ requires:

C, 65.4; H, 5.2; N, 7.6; S, 4.4%.

Found: C, 65.2; H, 5.1; N, 7.4; S, 4.4%.

Elution with EtOAc:light petroleum (2:3) gave

5 2,2'-dithiobis[N-(3-hydroxy-4-methoxycarbonylbenzyl)-
3-(3-indolyl)propanamide] (57) [V: $n = 2$; $R_1 = R_3 = H$,
 $R_2 = (CH_2)_2CONHCH_2Ph\{3-OH, 4-COOMe\}$] (0.38 g, 27%);
mp (MeOH) 183-185°C.

10 1H NMR ($CDCl_3$): δ 10.80 (1H, s, OH), 8.65 (1H, s, NH),
7.67 (1H, d, $J = 8.1$ Hz, ArH), 7.52 (1H, d, $J = 8.0$ Hz,
ArH), 7.27 (1H, d, $J = 7.7$ Hz, ArH), 7.15 (1H, ddd,
 $J = 8.1, 7.2, 0.9$ Hz, ArH), 7.01 (1H, ddd, $J = 7.9$,
7.2, 0.7 Hz, ArH), 6.55 (1H, d, $J = 1.5$ Hz, ArH), 6.52
15 (1H, dd, $J = 8.2, 1.5$ Hz, ArH), 5.10 (1H, t,
 $J = 5.9$ Hz, $NHCH_2$), 4.13 (2H, d, $J = 6.0$ Hz, $NHCH_2$),
3.94 (3H, s, OCH_3), 2.88, 1.94 (2x2H, 2xt, $J = 7.7$ Hz,
3- CH_2CH_2).

^{13}C NMR: δ 172.12 (s, CONH), 170.39 (s, $COOCH_3$),
161.55, 146.95, 137.29 (3xs, Ar), 130.09 (d, Ar),
20 127.01, 125.87 (2xs, Ar), 124.39 (d, Ar), 123.79 (s,
Ar), 120.16, 119.86, 118.34, 115.69, 111.37 (5xd, Ar),
111.20 (s, Ar), 52.31 (q, OCH_3), 42.82 (t, $NHCH_2$),
37.09 (t, 3- CH_2CH_2), 20.54 (t, 3- CH_2).

Analysis calculated for $C_{40}H_{38}N_4O_8S_2$ requires:

25 C, 62.7; H, 5.0; N, 7.3; S, 8.4%.

Found: C, 62.5; H, 4.9; N, 7.3; S, 8.4%.

Hydrolysis of 57 (0.28 g) with K_2CO_3 in MeOH/water
at 50°C for 5 hours, under nitrogen as above, gave an
oil. Chromatography on silica gel, eluting with
30 EtOAc:light petroleum (1:1) containing 1% AcOH, gave
2,2'-dithiobis[N-(4-carboxy-3-hydroxybenzyl)-
3-(3-indolyl)propanamide] (58) [VI: $n = 2$;
 $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONHCH_2Ph\{3-OH, 4-COOH\}$] (72 mg,
27%); mp (MeOH/dilute HCl) 160-163.5°C (dec).

-81-

- ¹H NMR (CD₃)₂SO): δ 11.39 (1H, s, NH), 8.03 (1H, t, J = 5.9 Hz, NHCH₂), 7.65 (1H, d, J = 8.1 Hz, ArH), 7.54 (1H, d, J = 8.0 Hz, ArH), 7.32 (1H, d, J = 8.2 Hz, ArH), 7.16 (1H, ddd, J = 8.1, 7.1, 1.0 Hz, ArH), 6.99 (1H, ddd, J = 7.8, 7.1, 0.7 Hz, ArH), 6.72 (1H, d, J = 1.3 Hz, ArH), 6.57 (1H, dd, J = 8.2, 1.4 Hz, ArH), 4.13 (2H, d, J = 5.9 Hz, NHCH₂), 2.75, 2.24 (2x2H, 2xt, J = 7.8 Hz, 3-CH₂CH₂).
- ¹³C NMR: δ 171.70 (s, CONH), 171.47 (s, COOH), 161.04, 147.83, 137.37 (3xs, Ar), 130.08 (d, Ar), 126.51, 125.11 (2xs, Ar), 123.25 (d, Ar), 122.42 (s, Ar), 119.49, 118.86, 117.73, 115.09, 111.41 (5xd, Ar), 111.21 (s, Ar), 41.67 (t, NHCH₂), 36.63 (t, 3-CH₂CH₂), 20.41 (t, 3-CH₂).
- Analysis calculated for C₃₈H₃₄N₄O₈S₂·H₂O requires:
C, 60.3; H, 4.8; N, 7.4; S, 8.5%.
Found: C, 60.2; H, 4.9; N, 7.1; S, 8.5%.

Compound 59 of Table 1

- 3-(3-Indolyl)propanoic acid [II: R₁ = R₃ = H, R₂ = (CH₂)₂COOH] (0.95 g) was treated with S₂Cl₂ as above, then the product mixture obtained after workup was treated successively with NaBH₄ then H₂O₂ as described above, to give crude 2,2'-dithiobis[3-(3-indolyl)propanoic acid] [VI: n = 2; R₁ = R₃ = H, R₂ = (CH₂)₂COOH] (1.12 g) as an oil. DEPC (98%, 1.00 mL) was added to a stirred solution of this oil, triethylamine (0.84 mL) and aniline (1.55 mL) in THF (15 mL) at 0°C, then the mixture was stirred at 20°C for 1 day. Dilute KOH (0.1 M, 100 mL) was added and the mixture stirred for 30 minutes (in an attempt to cleave the DEPC adduct and reform the disulfide), then the mixture extracted with CH₂Cl₂ (3 x 100 mL). Evaporation gave an oil which was partly purified by

-82-

chromatography on silica gel, eluting with EtOAc/light petroleum (2:1). The yellow disulfide was further purified by chromatography on fresh silica gel, eluting with CH₂Cl₂, then CHCl₃:EtOH (99:1), to give

5 2,2'-dithiobis[N-phenyl-3-(3-indolyl)propanamide] (59)
[VI: $n = 2$; $R_1 = R_3 = H$, $R_2 = (CH_2)_2CONHPh$] (0.23 g, 16% overall); mp (CH₂Cl₂/benzene) 181-182.5°C (an analytical sample recrystallized from CH₂Cl₂/light petroleum decomposed above 114°C).

10 ¹H NMR ((CD₃)₂CO): δ 10.52 (1H, s, NH), 8.88 (1H, s, NHPh), 7.64 (1H, d, $J = 8.0$ Hz, ArH), 7.56 (2H, dd, $J = 7.5, 0.9$ Hz, ArH), 7.37 (1H, d, $J = 8.2$ Hz, ArH), 7.24 (2H, dd, $J = 8.4, 7.5$ Hz, ArH(Ph)), 7.16 (1H, ddd, $J = 8.1, 7.1, 1.1$ Hz, ArH), 7.02 (2H, m, ArH), 3.04, 2.54 (2x2H, 2xm, 3-CH₂CH₂).

15 ¹³C NMR: δ 171.48 (s, CONH), 140.24, 138.80 (2xs, Ar), 129.37 (2xd, Ar), 128.17, 126.81 (2xs, Ar) 124.57, 124.02 (2xd, Ar), 123.86 (s, Ar), 120.62, 120.36 (2xd, Ar), 120.23 (2xbr d, Ar), 112.38 (d, Ar), 38.97 (t, 3-CH₂CH₂) 21.39 (t, 3-CH₂).

20 Analysis calculated for C₃₄H₃₀N₄O₂S₂·0.5H₂O requires:

C, 68.1; H, 5.2; N, 9.4; S, 10.7%.

Found: C, 68.3; H, 5.1; N, 9.3; S, 10.9%.

25 Compound 60 of Table 1

DEPC (98%, 0.72 mL) was added to a stirred solution of DL-N-acetyltryptophan (1.00 g) and benzylamine (2.0 mL) in DMF (10 mL) at 0°C, then the mixture was stirred at 20°C for 16 hours. The reaction was then quenched with water and extracted with EtOAc. Evaporation gave an oil which was chromatographed on silica gel. Elution with CH₂Cl₂ and EtOAc gave firstly foreruns, then DL- α -acetylamino-N-benzyl-3-(3-indolyl)-propanamide [II: $R_1 = R_3 = H$,

30

-83-

$R_2 = \text{CH}_2\text{CH}(\text{NHAc})\text{CONHCH}_2\text{Ph}$] (0.82 g, 60%);

mp (CH_2Cl_2 /light petroleum) 169-170°C.

^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 10.80 (1H, s, NH), 8.47 (1H, br t, $J = 5.8$ Hz, NHCH_2), 8.08 (1H, d, $J = 8.1$ Hz, CHNH), 7.61 (1H, d, $J = 7.8$ Hz, ArH), 7.33 (1H, d, $J = 8.1$ Hz, ArH), 7.26 (2H, dt, $J = 7.1, 1.5$ Hz, ArH), 7.20 (1H, dt, $J = 7.2, 1.5$ Hz, ArH), 7.13 (1H, m, H-2), 7.12 (2H, d, $J = 7.2$ Hz, ArH), 7.06 (1H, ddd, $J = 7.9, 7.1, 0.9$ Hz, ArH), 6.97 (1H, ddd, $J = 7.9, 7.0, 0.9$ Hz, ArH), 4.57 (1H, td, $J = 8.3, 5.7$ Hz, 3- CH_2CH), 4.28, 4.24 (2x1H, 2xdd, $J = 15.9, 5.9$ Hz, NHCH_2), 3.13 (1H, dd, $J = 14.4, 5.6$ Hz, 3-CH), 2.93 (1H, dd, $J = 14.4, 8.6$ Hz, 3-CH), 1.80 (3H, s, COCH_3).

^{13}C NMR: δ 171.59 (s, COCH_3), 169.02 (s, CONH), 139.18, 135.99 (2xs, Ar), 128.06 (d, 2C, Ar), 127.21 (s, Ar), 126.87 (d, 2C, Ar), 126.49, 123.47, 120.75, 118.39, 118.10, 111.17 (6xd, Ar), 110.11 (s, Ar), 53.53 (d, CH), 41.91 (t, NHCH_2), 27.92 (t, 3- CH_2), 22.50 (q, CH_3).

Analysis calculated for $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_2$ requires:

C, 71.6; H, 6.3; N, 12.5%.

Found: C, 71.5; H, 6.4; N, 12.6%.

Acidification of the aqueous portion with dilute HCl, extraction with EtOAc and evaporation gave *N*-acetyltryptophan (0.30 g, 30%); mp (EtOAc/light petroleum) 204-206°C.

The above α -acetamide (1.25 g) was treated with S_2Cl_2 as above, then the product mixture obtained after workup was treated successively with NaBH_4 then H_2O_2 as described above. The resulting oil was chromatographed on silica gel, eluting with CH_2Cl_2 :EtOAc (2:1) to give firstly 2,2'-thiobis[α -acetylamino-*N*-benzyl-3-(3-indolyl)propanamide] [VI: $n = 1$; $R_1 = R_3 = \text{H}$, $R_2 = \text{CH}_2\text{CH}(\text{NHAc})\text{CONHCH}_2\text{Ph}$] (0.30 g, 23%) as a mixture

-84-

of diastereoisomers; mp (EtOAc/light petroleum)
190-194°C.

^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 10.97, 10.94 (2x1H, 2xs, NH),
8.50, 8.48 (2x1H, 2xbr t, $J = 5.8$ Hz, NHCH_2), 8.17,
5 8.15 (2x1H, d, $J = 8.4$ Hz, CHNH), 7.63 (2x1H, d,
 $J = 7.7$ Hz, ArH), 7.3-6.9 (2x8H, m, ArH), 4.75 (2x1H,
m, 3- CH_2CH), 4.27, 4.19 (4x1H, 2xdd, $J = 16.1, 5.7$ Hz,
 NHCH_2), 3.44 (2x1H, m, 3-CH), 3.18 (2x1H, m, 3-CH),
1.79 (2x3H, 2xs, COCH_3).

10 ^{13}C NMR: δ 171.20, 171.18 (2xs, COCH_3), 169.13 (s, 2C,
CONH), 138.83, 138.79 (2xs, Ar), 136.66 (s, 2C, Ar),
128.03, 128.01 (2xd, 2x2C, Ar), 127.42 (s, 2C, Ar),
126.96, 126.91 (2d, 2x2C, Ar), 126.51, 126.48 (2xd,
Ar), 124.58, 124.55 (2xs, Ar), 121.97 (d, 2x2C, Ar),
15 119.02, 118.98 (2xd, Ar), 118.66 (d, 2C, Ar), 115.01,
114.94 (2xs, Ar), 110.79 (d, 2C, Ar), 53.66, 53.59
(2xd, 3- CH_2CH), 42.13 (t, 2C, NHCH_2), 28.14, 28.07
(2xt, 3- CH_2), 22.52 (q, 2C, CH_3).

Analysis calculated for $\text{C}_{40}\text{H}_{40}\text{N}_6\text{O}_4\text{S} \cdot 0.5\text{H}_2\text{O}$ requires:

20 C, 67.7; H, 5.8; N, 11.9; S, 4.5%.

Found: C, 67.7; H, 5.8; N, 11.9; S, 5.1%.

Elution with CH_2Cl_2 :EtOAc (1:2) gave

2,2'-dithiobis[α -acetylamino-N-benzyl-3-(3-indolyl)-
propanamide] (60) [VI: $n = 2$; $\text{R}_1 = \text{R}_3 = \text{H}$,

25 $\text{R}_2 = \text{CH}_2\text{CH}(\text{NHAc})\text{CONHCH}_2\text{Ph}$] (0.84 g, 62%) as a yellow
oil (a mixture of diastereoisomers). Crystallizations
from CH_2Cl_2 /light petroleum gave a single pair of
diastereoisomers; mp 140-144°C (dec).

^1H NMR (CDCl_3): δ 9.16 (1H, s, NH), 7.51 (1H, d,
30 $J = 8.1$ Hz, ArH), 7.2-7.0 (6H, m, ArH), 6.89 (2H, m,
ArH), 6.76 (1H, d, $J = 7.2$ Hz, CHNH), 6.16 (1H, t,
 $J = 5.8$ Hz, NHCH_2), 4.64 (1H, q, $J = 7.2$ Hz, 3- CH_2CH),
4.20, 4.12 (2x1H, 2xdd, $J = 14.8, 5.9$ Hz, NHCH_2), 3.13

-85-

(1H, dd, $J = 14.0, 7.1$ Hz, 3-CH), 2.96 (1H, dd, $J = 14.0, 7.3$ Hz, 3-CH), 1.84 (3H, s, COCH₃).

Analysis calculated for C₄₀H₄₀N₆O₄S₂·0.5H₂O requires:

C, 64.8; H, 5.5; N, 11.3; S, 8.6 %.

5 Found: C, 65.0; H, 5.4; N, 11.3; S, 8.8%.

Crystallizations from EtOAc/light petroleum gave the other pair of diastereoisomers of 60; mp 154.5-157.5°C (dec).

10 ¹H NMR (CDCl₃): δ 9.27 (1H, s, NH), 7.42 (1H, d, $J = 8.0$ Hz, ArH), 7.28-7.12 (6H, m, ArH), 7.04 (1H, dd, $J = 7.8, 7.0$ Hz, ArH), 6.75 (2H, m, ArH), 6.45 (1H, br d, $J = 7.1$ Hz, CHNH), 5.90 (1H, br s, NHCH₂), 4.41 (1H, q, $J = 7.4$ Hz, 3-CH₂CH), 4.17 (1H, dd, $J = 14.8, 6.0$ Hz, NHCH), 4.08 (1H, dd, $J = 14.8, 5.0$ Hz, NHCH), 2.99 (1H, dd, $J = 14.0, 6.9$ Hz, 3-CH), 2.93 (1H, dd, $J = 13.9, 7.6$ Hz, 3-CH), 1.82 (3H, s, COCH₃).

15 ¹³C NMR: δ 170.74 (s, COCH₃), 169.92 (s, CONH), 137.42, 137.28 (2xs, Ar), 128.58 (d, 2C, Ar), 127.59 (s, Ar), 127.51 (d, 2C, Ar), 127.40 (d, Ar), 126.26 (s, Ar), 124.39, 120.37, 119.51 (3xd, Ar), 118.96 (s, Ar), 111.51 (d, Ar), 54.63 (d, 3-CH₂CH), 43.70 (t, NHCH₂), 28.87 (t, 3-CH₂), 23.23 (q, CH₃).

20 Analysis calculated for C₄₀H₄₀N₆O₄S₂ requires:

C, 65.6; H, 5.5; N, 11.5; S, 8.7%.

25 Found: C, 65.4; H, 5.6; N, 11.5; S, 8.7%.

In DMSO solution, both pure diastereomers reverted to a 1:1 mixture of diastereoisomers by disulfide exchange within 3 minutes.

30 Compounds 61 and 62 of Table 1

Ethyl trifluoroacetate (1.7 mL) was added to a stirred solution of DL-tryptophan (2.3 g) and triethylamine (1.6 mL) in DMF (5 mL), then the flask was sealed and purged with nitrogen, and the mixture

-86-

stirred at 20°C for 1 day (method of Curphey TJ, J. Org. Chem. 1979;44:2805). Excess reagents were removed under vacuum, then triethylamine (1.9 mL) and DMF (10 mL) were added, and the mixture cooled to 0°C.

5 DEPC (98%, 2.0 mL) was added, followed by benzylamine (1.72 mL), then the mixture was stirred under nitrogen at 20°C for 1 day. The resulting solution was diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL). Evaporation gave an oil which was

10 purified by chromatography on silica gel, eluting with EtOAc:light petroleum (1:1), to give DL-N-benzyl- α -trifluoroacetyl-amino-3-(3-indolyl)propanamide [II: $R_1 = R_3 = H$, $R_2 = CH_2CH(NHCOCF_3)CONHCH_2Ph$] (2.21 g, 50%); mp (EtOAc/light petroleum) 181-183°C.

15 1H NMR ($(CD_3)_2SO$): δ 10.84 (1H, s, NH), 9.65 (1H, br s, CHNH), 8.79 (1H, t, $J = 5.5$ Hz, NHCH₂), 7.67 (1H, d, $J = 7.8$ Hz, ArH), 7.34 (1H, d, $J = 8.0$ Hz, ArH), 7.30 (2H, t, $J = 7.2$ Hz, ArH), 7.23 (1H, t, $J = 7.3$ Hz, ArH), 7.18 (2H, d, $J = 7.5$ Hz, ArH), 7.15 (1H, d, $J = 2.2$ Hz, H-2), 7.07 (1H, ddd, $J = 8.0, 7.1, 0.9$ Hz, ArH), 6.98 (1H, dd, $J = 7.8, 7.0$ Hz, ArH), 4.63 (1H, br m, 3-CH₂CH), 4.32 (2H, d, $J = 5.8$ Hz, NHCH₂), 3.25 (1H, dd, $J = 14.5, 5.0$ Hz, 3-CH), 3.12 (1H, dd, $J = 14.5, 9.9$ Hz, 3-CH).

20 ^{13}C NMR: δ 169.89 (s, CONH), 156.14, (q, $J_{CF} = 36.5$ Hz, $COCF_3$), 138.92, 135.97 (2xs, Ar), 128.17, 126.95 (2xd, 2x2C, Ar), 126.95 (s, Ar) 126.68, 123.77, 120.86, 118.36, 118.17 (5xd, Ar), 115.69 (q, $J_{CF} = 288$ Hz, CF_3), 111.24 (d, Ar), 109.41 (s, Ar), 54.24 (d, 3-CH₂CH), 42.11 (t, NHCH₂), 27.08 (t, 3-CH₂).

30 Analysis calculated for $C_{20}H_{18}F_3N_3O_2$ requires:
C, 61.7; H, 4.6; N, 10.8%.
Found: C, 61.9; H, 4.9; N, 10.9%.

-87-

Acidification of the aqueous portion with dilute HCl, then extraction with EtOAc (3 x 100 mL) and evaporation gave DL- α -trifluoroacetyl-amino-3-(3-indolyl)propanoic acid [II: $R_1 = R_3 = H$, $R_2 = CH_2CH(NHCOCF_3)COOH$] (0.72 g, 21%); mp (water) 155-157°C (Weygand F, Geiger R, Chem. Ber. 1956;89:647 record mp 162-163°C).

1H NMR ($(CD_3)_2SO$): δ 10.86 (1H, br s, NH), 9.75 (1H, br d, $J = 8.0$ Hz, CHNH), 7.55 (1H, d, $J = 7.8$ Hz, ArH), 7.34 (1H, d, $J = 8.1$ Hz, ArH), 7.14 (1H, d, $J = 2.3$ Hz, H-2), 7.07 (1H, ddd, $J = 8.0, 7.1, 0.9$ Hz, ArH), 6.99 (1H, ddd, $J = 7.9, 7.0, 0.9$ Hz, ArH), 4.51 (1H, ddd, $J = 10.2, 8.0, 4.2$ Hz, 3- CH_2CH), 3.32 (1H, dd, $J = 14.8, 4.3$ Hz, 3-CH), 3.17 (1H, dd, $J = 14.8, 10.3$ Hz, 3-CH).

^{13}C NMR: δ 171.64 (s, COOH), 156.23 (q, $J_{CF} = 36.5$ Hz, $COCF_3$), 136.01, 126.85 (2xs, Ar), 123.45, 120.93, 118.35, 117.90 (4xd, Ar), 117.09, 115.66 (q, $J_{CF} = 288$ Hz, CF_3), 111.36 (d, Ar), 109.56 (s, Ar), 53.58 (d, 3- CH_2CH), 25.88 (t, 3- CH_2).

The above α -trifluoroacetamide (2.15 g) was treated with S_2Cl_2 as above, then the product mixture obtained after workup was chromatographed directly on silica gel. Elution with CH_2Cl_2 and $CH_2Cl_2:EtOAc$ (19:1) gave foreruns, including mono- and trisulfides, then 2,2'-dithiobis[N-benzyl- α -trifluoroacetyl-amino-3-(3-indolyl)propanamide] (61) [VI: $n = 2$; $R_1 = R_3 = H$, $R_2 = CH_2CH(NHCOCF_3)CONHCH_2Ph$] (1.01 g, 44%) as a yellow oil (a mixture of diastereoisomers). A subsample crystallized from EtOH was a single pair of diastereoisomers; mp 160-164°C (decomposed).

1H NMR ($CDCl_3$): δ 8.76 (1H, s, NH), 7.57 (1H, d, $J = 8.0$ Hz, CHNH), 7.43 (1H, d, $J = 7.9$ Hz, ArH), 7.3-7.0 (6H, m, ArH), 6.75 (2H, m, ArH), 5.49 (1H, t,

-88-

$J = 5.2$ Hz, NHCH_2), 4.26 (1H, td, $J = 7.9$, 6.4 Hz, 3- CH_2CH), 4.14 (1H, dd, $J = 14.8$, 5.8 Hz, NHCH_2), 4.00 (1H, dd, $J = 14.5$, 4.9 Hz, NHCH_2) 2.99 (1H, dd, $J = 14.0$, 8.4 Hz, 3-CH), 2.77 (1H, dd, $J = 14.0$, 5.9 Hz, 3-CH).

^{13}C NMR: δ 168.87 (s, CONH), 156.81 (q, $J_{\text{CF}} = 36.5$ Hz, COCF_3), 137.25, 136.61 (2xs, Ar), 128.73 (d, 2C, Ar), 127.71 (d, 3C, Ar), 126.96, 126.11 (2xs, Ar), 124.97, 120.95, 119.25 (3xd, Ar), 118.14 (s, Ar), 115.62 (q, $J_{\text{CF}} = 288$ Hz, CF_3), 111.49 (d, Ar), 54.67 (d, 3- CH_2CH), 44.02 (t, NHCH_2), 28.22 (t, 3- CH_2).

Analysis calculated for $\text{C}_{40}\text{H}_{34}\text{F}_6\text{N}_6\text{O}_4\text{S}_2 \cdot 0.5\text{H}_2\text{O}$ requires:

C, 56.5; H, 4.1; N, 9.9; S, 7.5%.

Found: C, 56.6; H, 4.3; N, 9.8; S, 7.6%.

The trifluoroacetamide disulfide (61) (0.80 g) was treated with excess NaBH_4 at 20°C as above, then the resulting oil was chromatographed on alumina. Elution with $\text{CHCl}_3:\text{EtOH}$ (99:1) gave foreruns, then elution with $\text{CHCl}_3:\text{EtOH}$ (98:2) gave 2,2'-dithiobis[α -amino-*N*-benzyl-3-(3-indolyl)propanamide] (62) [VI: $n = 2$;

$\text{R}_1 = \text{R}_3 = \text{H}$, $\text{R}_2 = \text{CH}_2\text{CH}(\text{NH}_2)\text{CONHCH}_2\text{Ph}$] (0.14 g, 22%); mp (CH_2Cl_2 /light petroleum) $147\text{--}150^\circ\text{C}$ (decomposed).

^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 11.56 (1H, s, NH), 8.18 (1H, t, $J = 5.8$ Hz, NHCH_2), 7.61 (1H, d, $J = 7.8$ Hz, ArH), 7.36 (1H, d, $J = 8.1$ Hz, ArH), 7.33-6.95 (7H, m, ArH), 4.23, 4.13 (2x1H, 2xdd, $J = 15.2$, 5.8 Hz, NHCH_2), 3.41 (1H, br m, 3- CH_2CH), 2.93 (1H, dd, $J = 13.7$, 4.9 Hz, 3-CH), 2.64 (1H, br m, 3-CH), 1.7 (2H, br s, NH_2).

^{13}C NMR: δ 174.12 (s, CONH), 139.13, 137.38 (2xs, Ar), 128.06, 127.02 (2xd, 2x2C, Ar), 126.95, 126.71 (2xs, Ar), 126.51, 123.19, 119.62 (3xd, Ar), 119.18 (s, Ar), 118.87, 111.39 (2xd, Ar), 55.57 (d, 3- CH_2CH), 41.90 (t, NHCH_2), 30.58 (t, 3- CH_2).

-89-

Analysis calculated for $C_{36}H_{36}N_6O_2S_2 \cdot 0.5H_2O$ requires:

C, 65.8; H, 5.6; N, 12.8%.

Found: C, 65.8; H, 5.8; N, 12.6%.

5 Compound 63 of Table 1

Acetyl chloride (0.50 mL, 7.0 mmol) was added to a stirred solution of DL-3-(3-indolyl)lactic acid (1.00 g, 14.3 mmol) and Et_3N (2 mL, 14.3 mmol) in THF (5 mL) at 0°C. The mixture was stirred at 0°C for 7 hours, then at 20°C for 15 hours, quenched with water (100 mL), acidified with dilute HCl (to pH 2), then extracted with EtOAc (3 x 100 mL). Evaporation gave crude (ca. 90% pure) DL- α -acetoxy-3-(3-indolyl)-propanoic acid [II: $R_1 = R_3 = H$, $R_2 = CH_2CH(OAc)COOH$] (1.30 g) as an oil which was used directly.

1H NMR ($(CD_3)_2SO$): δ 10.88 (1H, s, NH), 7.54 (1H, d, $J = 7.8$ Hz, ArH), 7.33 (1H, d, $J = 8.0$ Hz, ArH), 7.17 (1H, br s, H-2), 7.06 (1H, dd, $J = 8.0, 7.1$ Hz, ArH), 6.99 (1H, t, $J = 7.4$ Hz, ArH), 5.06 (1H, dd, $J = 7.3, 4.9$ Hz, 3- CH_2CH), 3.22 (1H, dd, $J = 15.1, 4.5$ Hz, 3-CH), 3.16 (1H, dd, $J = 15.0, 7.7$ Hz, 3-CH), 2.00 (3H, s, $COCH_3$).

^{13}C NMR: δ 170.87, 169.96 (2xs, COOH, $OCOCH_3$), 136.04, 127.28 (2xs, Ar), 123.84, 120.94, 118.43, 118.33, 111.39 (5xd, Ar), 108.90 (s, Ar), 72.70 (d, 3- CH_2CH), 26.75 (t, 3- CH_2), 20.54 (q, CH_3).

HREIMS m/z calculated for $C_{13}H_{13}NO_4$:

247.0845 (M^+).

Found: 247.0848.

30 The above α -O-acetate (1.30 g of 90%, 4.4 mmol) and Et_3N (0.88 mL, 6.3 mmol) in DMF (10 mL) at 0°C was treated sequentially with DEPC (0.91 mL of 98%, 5.9 mmol) and benzylamine (0.69 mL, 6.3 mmol), and the mixture was stirred under nitrogen at 20°C for

-90-

18 hours. Workup and chromatography on silica gel, eluting with EtOAc/light petroleum (1:2 then 1:1) gave DL- α -acetoxy-N-benzyl-3-(3-indolyl)propanamide [II: $R_1 = R_3 = H$, $R_2 = CH_2CH(OAc)CONHCH_2Ph$] (0.29 g, 18%) as an oil.

1H NMR ($CDCl_3$): δ 8.05 (1H, s, NH), 7.60 (1H, d, $J = 7.9$ Hz, ArH), 7.37 (1H, dt, $J = 8.1, 0.9$ Hz, ArH), 7.26-7.21 (3H, m, ArH), 7.20 (1H, ddd, $J = 8.1, 7.0, 1.1$ Hz, ArH), 7.12 (1H, ddd, $J = 8.0, 7.0, 1.0$ Hz, ArH), 6.97 (1H, d, $J = 2.4$ Hz, H-2), 6.94 (2H, m, ArH), 6.07 (1H, t, $J = 5.8$ Hz, $NHCH_2$), 5.47 (1H, t, $J = 5.4$ Hz, 3- CH_2CH), 4.38 (1H, dd, $J = 14.9, 6.1$ Hz, $NHCH$), 4.29 (1H, dd, $J = 14.9, 5.5$ Hz, $NHCH$), 3.41 (2H, d, $J = 5.5$ Hz, 3- CH_2), 2.06 (3H, s, $COCH_3$).

^{13}C NMR: δ 169.63, 169.33 (2xs, CONH, $OCOCH_3$), 137.56, 136.05 (2xs, Ar), 128.55 (d, 2C, Ar), 127.75 (s, Ar), 127.60 (d, 2C, Ar), 127.40, 123.43, 122.08, 119.61, 118.92, 111.13 (6xd, Ar), 109.83 (s, Ar), 74.56 (d, 3- CH_2CH), 43.12 (t, $NHCH_2$), 27.42 (t, 3- CH_2), 21.09 (q, CH_3).

HREIMS m/z calculated for $C_{20}H_{20}N_2O_3$:

336.1474 (M^+).

Found: 336.1471.

Unreacted α -acetoxy-3-(3-indolyl)propanoic acid (0.68 g, 52%) was also recovered.

Alternative Preparation of Above Acetoxypropanamide

A solution of $SnCl_4$ (5.4 mL, 46 mmol) in CCl_4 (50 mL) was added dropwise to a stirred solution of indole (5.4 g, 46 mmol) and N-benzyl-2,3-epoxypropanamide (Dolzani L, Tamaro M, Monti-Bragadin C, Cavicchionz G, Vecchiati G, D'Angeli F, Mutation Res. 1986;172:37) (14 g of 85%, 67 mmol) in CCl_4 (100 mL) at $-5^\circ C$ (method of

-91-

Entzeroth M, Kunczik T, Jaenicke L, Liebig's Ann. Chim. 1983:226). The mixture was stirred at 20°C for 16 hours, then diluted with CHCl_3 (100 mL) and 10% NaHCO_3 (250 mL) and stirred vigorously for 4 hours.

5 The aqueous portion was separated and extracted with CH_2Cl_2 (2 x 100 mL), and the combined organic extracts were washed with water, dried, and the solvents removed. The resulting oil was chromatographed on silica gel, eluting with CH_2Cl_2 /light petroleum (1:1) to yield unreacted indole (1.27 g, 24%). Elution with CH_2Cl_2 gave mixtures, then CH_2Cl_2 /EtOAc (4:1) gave a crude product. This was crystallized successively from CH_2Cl_2 /light petroleum, then CH_2Cl_2 /benzene/light petroleum to give DL-N-benzyl- α -hydroxy-3-(3-indolyl)-propanamide [II: $R_1 = R_3 = \text{H}$, $R_2 = \text{CH}_2\text{CH}(\text{OH})\text{CONHCH}_2\text{Ph}$] (0.70 g, 5%); mp 127-128.5°C.

15 ^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 10.79 (1H, s, NH), 8.20 (1H, t, $J = 6.2$ Hz, NHCH_2), 7.56 (1H, d, $J = 7.8$ Hz, ArH), 7.34 (1H, d, $J = 8.1$ Hz, ArH), 7.24 (2H, m, ArH), 7.19 (1H, m, ArH), 7.12 (1H, d, $J = 2.3$ Hz, H-2), 7.10 (1H, m, ArH), 7.05 (1H, ddd, $J = 8.0, 7.0, 1.0$ Hz, ArH), 6.96 (1H, ddd, $J = 7.9, 7.0, 0.9$ Hz, ArH), 5.54 (1H, d, $J = 5.7$ Hz, OH), 4.26 (2H, d, $J = 6.2$ Hz, NHCH_2), 4.19 (1H, ddd, $J = 7.5, 5.7, 4.3$ Hz, 3- CH_2CH), 3.14 (1H, dd, $J = 14.5, 4.1$ Hz, 3-CH), 2.91 (1H, dd, $J = 14.5, 7.6$ Hz, 3-CH).

20 ^{13}C NMR: δ 173.59 (s, CONH), 139.40, 135.93 (2xs, Ar), 128.00 (d, 2C, Ar), 127.60 (s, Ar), 126.95 (d, 2C, Ar), 126.42, 123.58, 120.56, 118.60, 117.97, 111.05 (6xd, Ar), 110.53 (s, Ar), 71.86 (d, 3- CH_2CH), 41.60 (t, NHCH_2), 30.33 (t, 3- CH_2).

30 Analysis calculated for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2 \cdot 0.25\text{H}_2\text{O}$ requires:

C, 72.4; H, 6.2; N, 9.4%.

Found: C, 72.4; H, 6.0; N, 9.3%.

-92-

This α -hydroxypropanamide (0.62 g, 2.1 mmol) was stirred with pyridine (1.5 mL, 18.5 mmol) and Ac_2O (1.7 mL, 18.0 mmol) at 20°C for 17 hours. The mixture was partitioned between water and CH_2Cl_2 , and worked up to give a quantitative yield of DL- α -acetoxy-N-benzyl-3-(3-indolyl)propanamide [II: $\text{R}_1 = \text{R}_3 = \text{H}$, $\text{R}_2 = \text{CH}_2\text{CH}(\text{OAc})\text{CONHCH}_2\text{Ph}$].

This compound (1.07 g) was treated with S_2Cl_2 as above, and the resulting product mixture chromatographed on silica gel, eluting with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ (19:1), to give firstly 2,2'-thiobis-[α -acetoxy-N-benzyl-3-(3-indolyl)propanamide] [VI: $n = 1$, $\text{R}_1 = \text{R}_3 = \text{H}$, $\text{R}_2 = \text{CH}_2\text{CH}(\text{OAc})\text{CONHCH}_2\text{Ph}$] (0.19 g, 17%) as a mixture of diastereoisomers; mp (MeOH/dilute HCl) 105-109°C.

^1H NMR (CDCl_3): δ 10.09, 10.06 (2x1H, 2xs, NH), 7.61, 7.60 (2x1H, 2xd, $J = 7.9$ Hz, ArH), 7.24 (2x1H, d, $J = 8.2$ Hz, ArH), 7.14-7.00 (2x5H, m, ArH), 6.78, 6.70 (2x2H, 2xm, ArH), 6.27, 6.26 (2x1H, 2xt, $J = 5.8$ Hz, NHCH_2), 5.72 (1H, dd, $J = 7.0$, 6.0 Hz, 3- CH_2CH), 5.69 (1H, t, $J = 6.1$ Hz, 3- CH_2CH), 4.30, 4.27 (2x1H, 2xdd, $J = 15.0$, 5.8 Hz, NHCH), 4.23, 4.21 (2x1H, 2xdd, $J = 15.0$, 5.4 Hz, NHCH), 3.67 (1H, dd, $J = 14.5$, 7.0 Hz, 3-CH), 3.65 (1H, dd, $J = 14.7$, 5.8 Hz, 3-CH), 3.60 (1H, dd, $J = 14.7$, 6.3 Hz, 3-CH), 3.53 (1H, dd, $J = 14.5$, 6.0 Hz, 3-CH) 2.12, 2.11 (2x3H, 2xs, COCH_3).
 ^{13}C NMR (CDCl_3): δ 169.87, 169.73 (2xs, 2x2C, COCH_3 , CONH), 137.09, 137.03, 136.70, 136.65 (4xs, Ar), 128.60, 128.56 (2xd, 2x2C, Ar), 127.48, 127.44 (2xd, Ar), 127.43, 127.39 (2xs, Ar), 127.31, 127.28 (2xd, 2x2C, Ar), 125.47, 125.40 (2xs, Ar), 122.95, 122.93 (2xd, Ar), 119.64 (d, 2C, Ar), 119.07, 118.88 (2xd, Ar), 113.92, 113.70 (2xs, Ar), 111.32 (d, 2C, Ar),

-93-

73.99, 73.77 (2xd, 3-CH₂CH), 43.31 (t, 2C, NHCH₂),
28.00 (t, 2C, 3-CH₂), 21.19, 21.13 (2xq, CH₃).

Analysis calculated for C₄₀H₃₈N₄O₂S requires:

C, 68.4; H, 5.4; N, 8.0; S, 4.6%.

5 Found: C, 68.2; H, 5.6; N, 8.0; S, 4.8%.

Elution with CH₂Cl₂/EtOAc (9:1) gave
2,2'-dithiobis[α-acetoxy-N-benzyl-3-(3-indolyl)-
propanamide] (63) [VI: n = 2, R₁ = R₃ = H,
R₂ = CH₂CH(OAc)CONHCH₂Ph] (0.76 g, 65%) as a yellow oil
10 (mixture of diastereoisomers). A subsample
crystallized from CH₂Cl₂/dilute HCl as a single pair of
diastereoisomers; mp 120-124°C (dec).

¹H NMR (CDCl₃): δ 8.64 (1H, s, NH), 7.60 (1H, d,
J = 7.9 Hz, ArH), 7.27-7.15 (4H, m, ArH), 7.12, 7.11
15 (2x1H, 2xt, J = 8.1 Hz, ArH), 6.91 (2H, m, ArH), 6.12
(1H, t, J = 5.6 Hz, NHCH₂), 5.41 (1H, t, J = 6.2 Hz,
3-CH₂CH), 4.30, 4.24 (2x1H, 2xdd, J = 14.8, 5.71 Hz,
NHCH₂), 3.31 (1H, dd, J = 14.5, 5.8 Hz, 3-CH), 3.17
(1H, dd, J = 14.5, 6.6 Hz, 3-CH), 1.99 (3H, s, COCH₃).
20 ¹³C NMR (CDCl₃): δ 169.65, 168.96 (2xs, CONH, COCH₃),
137.50, 137.05 (2xs, Ar), 128.63 (d, 2C, Ar), 127.81
(s, Ar), 127.68 (d, 2C, Ar), 127.49 (d, Ar), 126.85 (s,
Ar), 124.30, 120.30, 120.03 (3xd, Ar), 117.87 (s, Ar),
111.33 (d, Ar), 74.06 (d, 3-CH₂CH), 43.30 (t, NHCH₂),
25 27.45 (t, 3-CH₂), 21.18 (q, CH₃).

Analysis calculated for C₄₀H₃₈N₄O₂S₂ requires:

C, 65.4; H, 5.2; N, 7.6; S, 8.7%.

Found: C, 65.2; H, 5.2; N, 7.8; S, 8.8%.

30 Compound 64 of Table 1

Hydrolysis of 63 with excess KHCO₃ in aqueous MeOH
at 20°C for 2 hours gave 2,2'-dithiobis[α-hydroxy-
N-(phenylmethyl)-1H-indole-3-propanamide] (64)
[II: R₁ = R₃ = H, R₂ = CH₂CH(OH)COOH] as an oil

-94-

(mixture of diastereomers) in essentially quantitative yield. Crystallization from CH_2Cl_2 /light petroleum gave a single pair of diastereomers (66% yield); mp 120-125°C.

5 ^1H NMR (CDCl_3): δ 7.61 (1H, d, $J = 8.0$ Hz, ArH),
7.33-7.17 (5H, m, ArH), 7.12 (2H, dd, $J = 7.8, 1.5$ Hz,
ArH), 7.09 (1H, ddd, $J = 8.1, 5.4, 2.7$ Hz, ArH), 6.80
(1H, t, $J = 5.8$ Hz, NHCH_2), 4.33, 4.27 (2x1H, 2xdd,
10 $J = 14.8, 5.9$ Hz, NHCH_2), 3.78 (1H, ddd, $J = 9.5, 5.4,$
3.4 Hz, 3- CH_2CH), 3.30 (1H, d, $J = 5.4$ Hz, OH), 3.24
(1H, dd, $J = 14.4, 3.4$ Hz, 3-CH), 2.88 (1H, dd,
 $J = 14.3, 9.5$ Hz, 3-CH).

Analysis calculated for $\text{C}_{36}\text{H}_{34}\text{N}_4\text{O}_4\text{S}_2$ requires:

C, 66.1; H, 5.3; N, 8.6; S, 9.6%.

15 Found: C, 66.5; H, 5.2; N, 8.6; S, 9.8%

EXAMPLE C

Preparation of Compounds 5 and 33 of Table 1 by the Method Outlined in Scheme 3

20 1-Methyl-2-indolinone [VII: $\text{R}_1 = \text{H}, \text{R}_3 = \text{Me}$] was
condensed with diethyl oxalate in NaOEt/EtOH , to give
ethyl 1-methyl isatylidenehydroxyacetate
[VIII: $\text{R}_1 = \text{H}, \text{R}_3 = \text{Me}, \text{R} = \text{COOEt}$] (82% yield);
mp 62-64°C (according to the method of Porter JC,
25 Robinson R, Wyler M, J. Chem. Soc. 1941:620, who report
mp 81°C). The above acetate [VIII: $\text{R}_1 = \text{H}, \text{R}_3 = \text{Me},$
 $\text{R} = \text{COOEt}$] (2.30 g) was hydrogenated in glacial AcOH
(150 mL) containing concentrated H_2SO_4 (1 mL) and 5%
Pd/C catalyst (5 g) for 1 day. The reaction mixture
30 was filtered onto NaOAc (4 g) and the solvent removed
under reduced pressure. The residue was partitioned
between CH_2Cl_2 and water, then the aqueous phase
re-extracted with CH_2Cl_2 . The CH_2Cl_2 extracts were
combined, washed with water, the solvent removed, and

-95-

the residue was chromatographed on silica gel. Elution with CH_2Cl_2 gave ethyl 2-(1-methyl-2-oxo-3-indoliny)-acetate [III: $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CH}_2\text{COOEt}$, $\text{R}_3 = \text{Me}$] as an oil (1.23 g, 57%).

- 5 ^1H NMR (CDCl_3): δ 7.29 (1H, t, $J = 7.7$ Hz, ArH), 7.26 (1H, d, $J = 7.5$ Hz, ArH), 7.03 (1H, t, $J = 7.5$ Hz, ArH), 6.84 (1H, d, $J = 7.7$ Hz, ArH), 4.15, 4.11 (2x1H, 2xdq, $J = 10.8$, 7.1 Hz, COOCH_2), 3.79 (1H, dd, $J = 8.0$, 4.4 Hz, H-3), 3.23 (3H, s, NCH_3), 3.07 (1H, dd, $J = 16.8$, 4.4 Hz, CH_2CO), 2.78 (1H, dd, $J = 16.8$, 8.1 Hz, CH_2CO), 1.20 (3H, t, $J = 7.1$ Hz, OCH_2CH_3).
- 10 ^{13}C NMR (CDCl_3): δ 176.72 (s, CONCH_3), 171.02 (COOCH_2), 144.35 (s, ArH), 128.27 (d, ArH), 128.18 (s, ArH), 123.80, 122.45, 108.01 (3xd, ArH), 60.85 (t, OCH_2), 41.83 (d, C-3), 34.94 (t, CH_2CO), 26.28 (q, NCH_3), 14.05 (q, OCH_2CH_3).
- 15

- The above oxoacetate [III: $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CH}_2\text{COOEt}$, $\text{R}_3 = \text{Me}$] was treated with P_2S_5 as described in Example A, then chromatographed on silica gel, with CH_2Cl_2 /light petroleum (3:2) eluting ethyl 2-(1-methyl-2-thioxo-3-indoliny)acetate [IV: $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CH}_2\text{COOEt}$, $\text{R}_3 = \text{Me}$] (5) (90% yield); mp (benzene/light petroleum) 47-48°C.
- 20 ^1H NMR (CDCl_3): δ 7.35 (2H, m, ArH), 7.16 (1H, td, $J = 7.5$, 0.8 Hz, ArH), 7.01 (1H, dd, $J = 7.7$, 1.0 Hz, ArH), 4.15 (2H, q, $J = 7.1$ Hz, COOCH_2), 4.14 (1H, m, H-3), 3.65 (3H, s, NCH_3), 3.39 (1H, dd, $J = 17.0$, 4.1 Hz, CH_2CO), 2.83 (1H, dd, $J = 17.0$, 8.6 Hz, CH_2CO), 1.22 (3H, t, $J = 7.1$ Hz, OCH_2CH_3).
- 25 ^{13}C NMR (CDCl_3): δ 204.35 (s, CSNCH_3), 171.11 (s, COOCH_2), 145.73, 133.01 (2xs, ArH), 128.39, 124.34, 123.94, 109.46 (4xd, ArH), 60.85 (t, OCH_2), 53.44 (d, C-3), 38.66 (t, CH_2CO), 31.52 (q, NCH_3), 14.13 (q, OCH_2CH_3).
- 30

-96-

Analysis calculated for $C_{13}H_{15}NO_2S$ requires:

C, 62.7; H, 6.0; N, 5.6; S, 12.9%.

Found: C, 62.5; H, 6.2; N, 5.6; S, 12.8%.

5 A solution of crude 5 in EtOH was exposed to air for 2 weeks, during which time bis[ethyl 1-methylindolyl-3-acetate-(2)]disulfide [V: $R_1 = H$, $R_2 = CH_2COOEt$, $R_3 = Me$] (33) slowly separated as yellow needles (0.18 g, 26%); mp 117-119°C.

10 1H NMR ($CDCl_3$): δ 7.53 (1H, dt, $J = 8.0, 0.8$ Hz, ArH), 7.30 (1H, ddd, $J = 8.3, 6.3, 1.1$ Hz, ArH), 7.27 (1H, ddd, $J = 8.1, 1.6, 0.7$ Hz, ArH), 7.12 (1H, ddd, $J = 8.0, 6.2, 1.8$ Hz, ArH), 3.96 (2H, q, $J = 7.1$ Hz, $COOCH_2$), 3.54 (3H, s, NCH_3), 3.38 (2H, s, CH_2CO), 1.14 (3H, t, $J = 7.1$ Hz, OCH_2CH_3).

15 ^{13}C NMR ($CDCl_3$): δ 171.06 (s, $COOCH_2$), 138.45, 128.42, 126.47 (3xs, ArH), 124.33, 120.20, 120.07 (3xd, ArH), 117.59 (s, ArH), 109.93 (d, ArH), 60.70 (t, OCH_2), 30.99 (t, CH_2CO), 29.97 (q, NCH_3), 14.13 (q, OCH_2CH_3).

Analysis calculated for $C_{26}H_{28}N_2O_4S_2$ requires:

20 C, 62.9; H, 5.7; N, 5.7; S, 12.9%.

Found: C, 62.7; H, 5.6; N, 5.6; S, 13.0%.

Compounds 10 and 38 of Table 1

25 Similar reactions on 2-indolinone [VII: $R_1 = R_3 = H$], using diethyl malonate, gave ethyl 3-(2-oxo-3-indoliny)propanoate [III: $R_1 = R_3 = H$, $R_2 = (CH_2)_2COOEt$] (Julian PL, Printy HC, J. Am. Chem. Soc. 1953;75:5301). Reaction of this with P_2S_5 as described in Example A, followed by chromatography on silica gel, elution with CH_2Cl_2 , and crystallization from benzene/light petroleum over 2 days, gave
30 bis[ethyl indolyl-3-propanoate-(2)]disulfide [V: $R_1 = R_3 = H$, $R_2 = (CH_2)_2COOEt$] (38) (18% yield); mp 137-139°C.

-97-

¹H NMR (CDCl₃): δ 8.25 (1H, s, NH), 7.55 (1H, d, J = 8.0 Hz, ArH), 7.22 (2H, m, ArH), 7.11 (1H, ddd, J = 8.0, 5.0, 3.0 Hz, ArH), 4.02 (2H, q, J = 7.1 Hz, COOCH₂), 2.98, 2.46 (2x2H, 2xt, J = 7.9 Hz, CH₂CH₂CO), 1.16 (3H, t, J = 7.1 Hz, OCH₂CH₃).

¹³C NMR (CDCl₃): δ 173.03 (s, COOCH₂), 137.26, 127.22, 125.83 (3xs, ArH), 124.26 (d, ArH), 122.81 (s, ArH), 120.03, 119.63, 111.19 (3xd, ArH), 60.41 (t, COOCH₂), 35.20 (t, CH₂CO), 20.26 (t, 3-CH₂), 14.14 (q, OCH₂CH₃).

Analysis calculated for C₂₆H₂₈N₂O₄S₂ requires:

C, 62.9; H, 5.7; N, 5.6; S, 12.9%.

Found: C, 63.3; H, 5.9; N, 5.7; S, 13.0%.

Treatment of the mother liquors with NaBH₄ gave ethyl 3-(2-thioxo-3-indoliny)propanoate [IV:

R₁ = R₃ = H, R₂ = (CH₂)₂COOEt] (10) (56% yield) as an oil.

¹H NMR (CDCl₃): δ 10.40 (1H, s, NH), 7.31 (1H, d, J = 7.4 Hz, ArH), 7.27 (1H, td, J = 7.8, 0.7 Hz, ArH), 7.14 (1H, td, J = 7.5, 0.7 Hz, ArH), 7.01 (1H, d, J = 7.8 Hz, ArH), 4.07, 4.03 (2x1H, 2xdq, J = 10.8, 7.1 Hz, COOCH₂), 3.91 (1H, t, J = 5.4 Hz, H-3), 2.52 (2H, m, CH₂CH₂CO), 2.41 (1H, ddd, J = 15.8, 9.9, 5.9 Hz, CH₂CO), 2.10 (1H, ddd, J = 15.8, 9.1, 6.7 Hz, CH₂CO), 1.20 (3H, t, J = 7.1 Hz, OCH₂CH₃).

¹³C NMR (CDCl₃): δ 207.31 (s, CSNH), 172.96 (s, COOCH₂), 143.31, 133.15 (2xs, ArH), 128.40, 124.34, 124.07, 110.04 (4xd, ArH), 60.55 (t, OCH₂), 56.44 (d, C-3), 29.56, 28.16 (2xt, (CH₂)₂CO), 14.15 (q, OCH₂CH₃).

Analysis calculated for C₁₃H₁₅NO₂S requires:

C, 62.6; H, 6.1; N, 5.6; S, 12.9%.

Found: C, 62.3; H, 5.9; N, 5.6; S, 12.6%.

-98-

Compounds 12 of Table 1

Similar treatment of 1-methyl-2-indolinone, using diethyl malonate, and subsequent thiation, gave ethyl 3-(1-methyl-2-thioxo-3-indoliny)propanoate [IV:

5 $R_1 = H$, $R_2 = (CH_2)_2COOEt$, $R_3 = Me$] (12);

mp (benzene/light petroleum) 61-63°C.

1H NMR ($CDCl_3$): δ 7.35 (2H, m, ArH), 7.20 (1H, t, $J = 7.5$ Hz, ArH), 7.00 (1H, d, $J = 7.8$ Hz, ArH), 4.05, 4.02 (2x1H, 2xdq, $J = 10.8$, 7.1 Hz, $COOCH_2$), 3.92 (1H, t, $J = 5.4$ Hz, H-3), 3.63 (3H, s, NCH_3), 2.53 (2H, td, $J = 8.0$, 5.4 Hz, CH_2CH_2CO), 2.32, 2.01 (2x1H, 2xt, $J = 16.0$, 8.0 Hz, CH_2CH_2CO), 1.19 (3H, t, $J = 7.1$ Hz, CH_2CH_3).

^{13}C NMR ($CDCl_3$): δ 204.85 (s, $CSNCH_3$), 172.87 (s, $COOCH_2$), 145.89, 132.44 (2xs, ArH), 128.37, 124.30, 124.00, 109.49 (4xd, ArH), 60.43 (t, OCH_2), 56.29 (d, C3), 31.35 (q, NCH_3), 29.53, 28.46 (2xt, CH_3CH_2CO), 14.15 (q, OCH_2CH_3).

Analysis calculated for $C_{14}H_{17}NO_2S$ requires:

20 C, 63.9; H, 6.5; N, 5.3; S, 12.2%.

Found: C, 64.1; H, 6.7; N, 5.4; S, 12.0%.

Compounds 41 and 42 of Table 1

Similar treatment of 5-methyl-2-indolinone

25 [VII: $R_1 = 5-Me$, $R_3 = H$] gave bis[ethyl

5-methylindolyl-3-propanoate-(2)]disulfide [V:

$R_1 = 5-Me$, $R_2 = (CH_2)_2COOEt$, $R_3 = H$] (42) as a yellow solid; mp (benzene/petroleum ether) 138.5-139°C.

1H NMR ($CDCl_3$): 8.10 (1H, s, NH), 7.32 (1H, d, $J = 0.6$ Hz, H-4), 7.15 (1H, d, $J = 8.3$ Hz, H-7), 7.06 (1H, dd, $J = 8.3$, 1.4 Hz, H-6), 4.03 (2H, q, $J = 7.2$ Hz, CH_2CH_3), 3.02-2.85 (2H, m, $CH_2CH_2CO_2$), 2.51-2.36 (2H, m, $CH_2CH_2CO_2$), 2.43 (3H, s, $ArCH_3$), 1.18 (3H, t, $J = 7.2$ Hz, CH_2CH_3).

-99-

^{13}C NMR (CDCl_3): δ 173.1 (CO_2Et), 135.6, 129.3, 127.4, 125.9, 122.3 (C-2,3,5,8,9), 126.0, 119.1, 110.9 (C-4,6,7), 60.4 (OCH_2CH_3), 35.2 ($\text{CH}_2\text{CH}_2\text{CO}_2$), 21.5 (ArCH_3), 20.3 ($\text{CH}_2\text{CH}_2\text{CO}_2$), 14.1 (OCH_2CH_3).

5 Analysis calculated for $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_4\text{S}_2 \cdot 0.5\text{C}_6\text{H}_6$ requires:

C, 66.1; H, 6.3; N, 5.0; S, 11.4%.

Found: C, 66.2; H, 6.4; N, 5.0; S, 11.7%.

Ester hydrolysis of 42 as above gave

10 bis[5-methylindolyl-3-propanoic acid-(2)]disulfide
[V: $\text{R}_1 = 5\text{-Me}$, $\text{R}_2 = (\text{CH})_2\text{CO}_2\text{H}$, $\text{R}_3 = \text{H}$] (41) as
orange-brown prisms; mp (CH_2Cl_2 /petroleum ether)
91.5-95°C.

^1H NMR (CDCl_3): δ 7.98 (1H, s, NH), 7.33 (1H, s, H-4),
7.14 (1H, d, $J = 8.4$ Hz, H-7), 7.07 (1H, dd, $J = 8.4$,
15 1.3 Hz, H-6), 2.98 (2H, t, $J = 7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CO}_2$), 2.56
(2H, t, $J = 7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CO}_2$), 2.43 (3H, s, ArCH_3).

HREIMS m/z calculated for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_4\text{S}_2$ requires:

235.06670.

Found: m/z 235.06639.

20

Compounds 43 and 44 of Table 1

Similar treatment of 6-methyl-2-indolinone

[VII: $\text{R}_1 = 6\text{-Me}$, $\text{R}_3 = \text{H}$] gave bis[ethyl
6-methylindolyl-3-propanoate-(2)]disulfide [V:
25 $\text{R}_1 = 6\text{-Me}$, $\text{R}_2 = (\text{CH}_2)_2\text{COOEt}$, $\text{R}_3 = \text{H}$] (44) as a yellow
solid; mp 122-123.5°C.

^1H NMR (CDCl_3): δ 8.06 (1H, s, NH), 7.43 (1H, d,
 $J = 8.2$ Hz, H-4), 7.03-7.00 (1H, m, H-7), 6.97-6.92
(1H, m, H-5), 4.02 (2H, q, $J = 7.2$ Hz, CH_2CH_3),
30 2.98-2.91 (2H, m, $\text{CH}_2\text{CH}_2\text{CO}$), 2.48-2.42 (2H, m,
 $\text{CH}_2\text{CH}_2\text{CO}$), 2.44 (3H, s, ArHMe), 1.17 (3H, t,
 $J = 7.2$ Hz, CH_2CH_3).

^{13}C NMR (CDCl_3): δ 173.0 (CO_2Et), 137.7, 134.3, 125.2,
125.0, 122.9 (C-2,3,6,8,9), 121.9, 119.3 (C-4,5,7),

-100-

60.3 (OCH_2CH_3), 35.2 ($\text{CH}_2\text{CH}_2\text{CO}_2$), 21.8 (ArCH_3), 20.3 ($\text{CH}_2\text{CH}_2\text{CO}_2$), 14.1 (OCH_2CH_3).

Analysis calculated for $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_4\text{S}_2$ requires:

C, 64.1; H, 6.2; N, 5.3; S, 12.2%.

5 Found: C, 64.1; H, 6.2; N, 5.4; S, 12.0%.

Ester hydrolysis of the above as above gave bis[methylindolyl-3-propanoate-(2)]disulfide [V: $\text{R}_1 = 6\text{-Me}$, $\text{R}_2 = (\text{CH}_2)_2\text{COOEt}$, $\text{R}_3 = \text{H}$] (43) as yellow microcrystals; mp (CH_2Cl_2 /petroleum ether) 126-128°C.

10 ^1H NMR ($(\text{CD}_3)_2\text{CO}$): δ 10.34 (1H, br s, NH), 7.49 (1H, d, $J = 8.2$ Hz, H-4), 7.19 (H, s, H-7), 6.19 (1H, dd, $J = 8.2, 1.2$ Hz, H-5), 2.97-2.90 (2H, m, CHCH_2CO_2), 2.49-2.43 (2H, m, $\text{CH}_2\text{CH}_2\text{CO}_2$), 2.42 (3H, s, ArCH_3).

Analysis calculated for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_4\text{S}_2 \cdot \text{H}_2\text{O}$ requires:

15 C, 60.4; H, 5.9; N, 5.9%.

Found: C, 60.2; H, 5.3; N, 5.9%.

Compounds 45 and 46 of Table 1

Similar treatment of 7-methyl-2-indolinone

20 [VII: $\text{R}_1 = 7\text{-Me}$, $\text{R}_3 = \text{H}$] gave bis[ethyl 7-methylindolyl-3-propanoate-(2)]disulfide [V: $\text{R}_1 = 7\text{-Me}$, $\text{R}_2 = (\text{CH}_2)_2\text{COOEt}$, $\text{R}_3 = \text{H}$] (46) as a yellow solid; mp (benzene/petroleum ether) 120-122.5°C.

25 ^1H NMR (CDCl_3): δ 8.23 (1H, s, NH), 7.38 (1H, d, $J = 7.4$ Hz, ArH), 7.00 (1H, t, $J = 7.3$ Hz, H-5), 6.94 (1H, d, $J = 6.3$ Hz, ArH), 4.02 (2H, q, $J = 7.2$ Hz, CH_2CH_3), 3.16 (2H, t, $J = 7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CO}_2$), 2.71 (2H, t, $J = 7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CO}_2$), 1.96 (3H, s, ArCH_3), 1.23 (3H, t, $J = 7.2$ Hz, CH_2CH_3).

30 ^{13}C NMR (CDCl_3): δ 173.6 (CO_2Et), 136.9, 127.0, 124.8, 122.9, 121.0 (C-2,3,7,8,9), 124.3, 120.0, 117.0 (C-4,5,6), 60.6 (OCH_2CH_3), 35.3 ($\text{CH}_2\text{CH}_2\text{CO}_2$), 20.9 ($\text{CH}_2\text{CH}_2\text{CO}_2$), 16.0 (ArCH_3), 14.1 (OCH_2CH_3).

-101-

Analysis calculated for $C_{28}H_{32}N_2O_4S_2$ requires:

C, 64.1; H, 6.2; N, 5.3; S, 12.2%.

Found: C, 64.2; H, 6.4; N, 5.4; S, 12.0%.

Ester hydrolysis of 46 as above gave

5 bis[7-methylindolyl-3-propanoic acid-(2)]disulfide

[V: $R_1 = 7\text{-Me}$, $R_2 = (\text{CH}_2)_2\text{CO}_2\text{H}$, $R_3 = \text{H}$] (45) as green needles; mp (AcOH/petroleum ether) 172.5-175°C.

^1H NMR ($(\text{CD}_3)_2\text{CO}$): δ 10.37 (1H, br s, NH), 7.45 (1H, d, $J = 7.0$ Hz, ArH), 7.03-6.95 (2H, m, ArH), 3.01-2.94 (2H, m, $\text{CH}_2\text{CH}_2\text{CO}_2$), 2.50-2.42 (2H, m, $\text{CH}_2\text{CH}_2\text{CO}_2$), 2.49 (3H, s, ArCH_3).

Analysis calculated for $C_{24}H_{24}N_2O_4S_2$ requires:

C, 61.5; H, 5.2; N, 6.0%.

Found: C, 61.3; H, 5.1; N, 6.0%.

15

EXAMPLE D

Preparation of Compounds 21-23 and 70 of Table 1 by the Method Outlined in Scheme 4

20 Powdered Na_2CO_3 (0.70 g, 6.61 mmol) was added to a suspension of P_2S_5 (2.93 g, 6.61 mmol) in THF (40 mL) and the mixture was stirred vigorously at 20°C until homogeneous, and gas evolution had ceased (15 minutes). A solution of 1-methyl-2-indolinone [VII: $R_1 = R_3 = \text{Me}$] (0.80 g, 5.50 mmol) in THF (10 mL) was
25 added and stirring was continued for 18 hours. After pouring into brine, the mixture was extracted into EtOAc, worked up, and chromatographed on silica. Elution with EtOAc/petroleum ether (1:4) gave 1-methyl-2-indolinethione [IX: $R_1 = R_3 = \text{Me}$] (0.71 g, 87%); mp 108-109°C (Hino T, Tsuneoka K, Nakagawa M, Akaboshi S, Chem. Pharm. Bull. 1969;17:550 record
30 109-111°C).

A solution of the above 1-methyl-2-indolinethione (4.1 g) in THF (150 mL) was treated dropwise over

-102-

15 minutes with an ice-cooled suspension of NaH (57%, 1.4 g) in THF (100 mL). The mixture was stirred for 30 minutes, then a solution of phenyl isocyanate (3.5 g) in THF (50 mL) was added, and stirring continued for 3 hours at 20°C. The solvent was removed under vacuum, then the residue decomposed with ice-HCl, and extracted in CH₂Cl₂. Removal of the solvent gave an oil (6.0 g), which crystallized from ether. Two recrystallizations from THF-ether gave N-phenyl (1-methyl-2-thioxo-3-indoliny)lcarboxamide [IV: R₁ = H, R₂ = CONHPh, R₃ = Me] (21) (2.8 g, 39%) as a pale yellow solid; mp 149-151°C.

¹H NMR (CDCl₃): δ 10.36 (1H, s, NH), 7.87 (1H, d, J = 7.4 Hz, ArH), 7.60 (2H, d, J = 7.9 Hz, ArH), 7.41 (2H, t, J = 7.5 Hz, ArH), 7.31 (2H, m, ArH), 7.11 (1H, t, J = 7.3 Hz, ArH), 7.03 (1H, d, J = 7.8 Hz, ArH), 3.73 (3H, s, NCH₃).

Analysis calculated for C₁₆H₁₄N₂OS requires:

C, 68.1; H, 5.1; N, 9.9; S, 11.4%.

Found: C, 67.8; H, 5.1; N, 9.8; S, 11.4%.

A solution of 21 (200 mg) in CH₂Cl₂/MeOH (2:1) (30 mL) was stirred at 20°C for 5 days, then the solvents were removed under reduced pressure.

Chromatography on silica gel, eluting with CH₂Cl₂ then CHCl₃/EtOH (99:1), gave bis[N-phenyl 1-methylindolyl-3-carboxamide-(2)] disulfide [V: R₁ = H, R₂ = CONHPh, R₃ = Me] (70) (0.19 g, 95%); mp (benzene) 187-188°C.

¹H NMR (CDCl₃): δ 8.21 (1H, s, NH), 8.01 (1H, d, J = 8.1 Hz, ArH), 7.19 (1H, ddd, J = 8.1, 7.1, 0.9 Hz, ArH), 7.13 (4H, d, J = 4.3 Hz, Ph), 7.09 (1H, ddd, J = 8.1, 7.1, 0.9 Hz, ArH), 7.05 (1H, d, J = 8.1 Hz, ArH), 6.98 (1H, quin, J = 4.3 Hz, Ph), 3.77 (3H, s, NCH₃).

-103-

^{13}C NMR (CDCl_3): δ 161.57 (CO), 138.55, 137.95 (2xs), 128.64 (d), 127.41, 126.07 (2xs), 125.55, 122.28, 122.00 (4xd), 119.76 (s), 119.27, 110.14 (2xd), 30.33 (NCH_3).

5 Analysis calculated for $\text{C}_{32}\text{H}_{26}\text{N}_4\text{O}_2\text{S}_2$ requires:

C, 68.3; H, 4.6; N, 10.0; S, 11.4%.

Found: C, 68.9; H, 4.9; N, 9.6; S, 11.1%.

A solution of 21 (200 mg) in Me_2CO (20 mL) was treated with K_2CO_3 (0.12 g) and methyl iodide (0.14 g) and the mixture stirred at 20°C for 1 hour. CH_2Cl_2 (100 mL) was added, then the solution filtered and the solvents removed, to yield a brown oil (0.26 g). Chromatography on silica gel, eluting with CH_2Cl_2 , gave N-phenyl (1-methyl-2-methylthio-3-indolyl)carboxamide as an oil [X: $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CONHPh}$, $\text{R}_3 = \text{Me}$, $\text{R}_4 = \text{SMe}$] (22) (200 mg, 95%), which crystallized from $\text{MeOH}/\text{CH}_2\text{Cl}_2$ as a white solid; mp $116\text{--}118^\circ\text{C}$.

^1H NMR (CDCl_3): δ 9.99 (1H, s, NH), 8.58 (1H, d, $\text{J} = 8.0$ Hz, ArH), 7.75 (2H, d, $\text{J} = 7.6$ Hz, ArH), 7.38 (4H, m, ArH), 7.29 (1H, quin, $\text{J} = 4.3$ Hz, ArH), 7.12 (1H, t, $\text{J} = 7.4$ Hz, ArH), 3.95 (3H, s, NCH_3), 2.47 (3H, s, SCH_3).

^{13}C NMR (CDCl_3): δ 162.59 (s, CONH), 138.80, 137.46, 131.43 (3xs, ArH), 129.03 (2xd, ArH), 127.35 (s, ArH), 124.14, 123.67, 123.02, 122.24 (4xd, ArH), 119.86 (2xd, ArH), 114.04 (s, ArH), 109.69 (d, ArH), 30.23 (q, NCH_3), 20.50 (q, SCH_3).

Analysis calculated for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{OS}$ requires:

C, 68.9; H, 5.4; N, 9.5; S, 10.8%.

30 Found: C, 68.6; H, 5.5; N, 9.4; S, 10.8%.

Benzyl mercaptan (0.02 mL, 0.178 mmol) was added to a suspension of 70 (50 mg, 89 mmol) and BF_3 -etherate (1 drop) in CH_2Cl_2 (1 mL). After stirring at 20°C for 3 hours, the homogeneous mixture was poured into

-104-

saturated aqueous NaHCO₃, diluted with CH₂Cl₂ and worked up, and the residue was chromatographed on silica gel. Elution with CH₂Cl₂/petroleum ether (1:1) gave foreruns, and elution with CH₂Cl₂ elute benzyl

5 [N-phenyl 1-methylindolyl-3-carboxamide-(2)]disulfide [XI: R₁ = H, R₂ = CONHPh, R₃ = Me, R₄ = S₂CH₂Ph] (23) (39 mg, 54%); mp (CHCl₃/petroleum ether) 146-148°C.

¹H NMR: δ 8.95 (1H, br s, CONH), 8.47 (1H, dd, J = 7.7, 1.3 Hz, ArH-4), 7.66 (2H, dd, J = 7.5, 1.2 Hz, Ph), 7.40-7.07 (11H, m, ArH-5, -6, -7 and Ph), 3.90 (3H, s, NMe).

10 ¹³C NMR: δ 162.31 (CONHPh), 138.31 (s), 138.04 (s), 135.13 (s), 130.00 (s), 129.15, 129.06, 128.69, 127.83, 126.83 (s), 124.79, 123.94, 122.80, 122.36, 119.90, 109.92, 42.51 (CH₂Ph), 30.73 (NCH₃).

15 Analysis calculated for C₂₃H₂₀N₂S₂O requires:
C, 68.3; H, 5.0; N, 6.9; S, 15.9%.
Found: C, 68.4; H, 5.1; N, 6.9; S, 16.0%

20 Compound 71 of Table 1

Similarly was prepared, from 1-ethyl-2-indolinethione (Kendall JD, Ficken GE, British Patent 829,584, Chem. Abstr. 1960;54:12847h) and phenyl isocyanate, bis[N-phenyl 1-ethylindolyl-3-carboxamide-(2)]disulfide [V: R₁ = H, R₂ = CONHPh, R₃ = Et] (71) (25% yield); mp 200-202°C.

25 ¹H NMR (CDCl₃): δ 8.22 (1H, br, CONH), 7.98 (1H, d, J = 8.1 Hz, H-4), 7.18 (1H, t, J = 8.0 Hz, H-6), 7.11-7.04 (6H, m, H-5 and Ph), 6.95 (1H, dd, J = 8.0, 1.0 Hz, H-7), 4.32 (2H, q, J = 7.0 Hz, NCH₂CH₃), 1.36 (3H, t, J = 7.0 Hz, NCH₂CH₃).

30 ¹³C NMR: δ 161.73 (CONH), 137.91 (s), 137.44 (s), 128.55, 128.55, 128.35 (2s), 126.33 (s), 125.41,

-105-

123.47, 122.12, 122.07, 119.37, 110.19 (C-7), 38.86
(NCH₂CH₃), 15.23 (NCH₂CH₃).

Analysis calculated for C₃₄H₃₀N₄S₂O₂ requires:

C, 69.1; H, 5.1; N, 9.5; S, 10.8%.

5 Found: C, 68.9; H, 5.4; N, 9.5; S, 10.4%.

Compound 72 of Table 1

Similarly was prepared 4-chloro-1-methyl-
2-indolinethione [IX: R₁ = 4-Cl, R₃ = Me] (92% yield);
10 mp 147.5-149.5°C.

¹H NMR (CDCl₃): δ 7.29 (1H, t, J = 8.0 Hz, H-6), 7.13
(1H, d, J = 8.0 Hz, H-5), 6.86 (1H, d, J = 8.0 Hz,
H-7), 4.09 (2H, s, H-3), 3.60 (3H, s, NCH₃).

15 ¹³C NMR: δ 200.75 (C-2), 147.65 (s), 130.04 (s),
129.52, 127.44 (s), 124.34, 107.81 (C-7), 48.42 (C-3),
31.55 (NCH₃).

Analysis calculated for C₉H₈ClNS requires:

C, 54.7; H, 4.1; N, 7.1; S, 16.2%.

Found: C, 54.5; H, 4.3; N, 7.1; S, 16.0%.

20 Reaction of this with phenyl isocyanate as above
gave bis[N-phenyl 4-chloro-1-methylindolyl-
3-carboxamide-(2)]disulfide [V: R₁ = 4-Cl,
R₂ = CONHPh, R₃ = Me] (72) (21% yield); mp 225-228°C.

25 ¹H NMR (CDCl₃): δ 8.38 (1H, br, NH), 7.49 (1H, dd,
J = 7.9, 1.5 Hz, H-5), 7.12 (1H, t, J = 7.9 Hz, H-6),
7.08-7.05 (4H, m, CONHPh), 6.98 (1H, dd, J = 7.9,
1.5 Hz, H-7), 6.96 (1H, m, CONHPh), 3.77 (3H, s,
N-CH₃).

Analysis calculated for C₃₂H₂₄Cl₂N₄O₂S₂ requires:

30 C, 60.8; H, 3.8; N, 8.9; Cl, 11.2%.

Found: C, 60.7; H, 4.1; N, 8.7; Cl, 11.8%.

-106-

Compound 73 of Table 1

Similarly was prepared, from 5-chloro-1-methyl-2-indolinethione [IX: $R_1 = 5\text{-Cl}$, $R_3 = \text{Me}$]; mp 163-165°C (Baudin J-B, Julia SA, Lorne R, Bull. Soc. Chim. Fr. 1987:181-188 records mp 153-155°C) and phenyl isocyanate, bis[N-phenyl 5-chloro-1-methylindolyl-3-carboxamide-(2)]disulfide [V: $R_1 = 5\text{-Cl}$, $R_2 = \text{CONHPh}$, $R_3 = \text{Me}$] (73) (27% yield); mp 214-216°C. ^1H NMR (CDCl_3): δ 8.14 (1H, br, CONH), 7.94 (1H, d, $J = 1.8$ Hz, H-4), 7.12 (4H, br, ArH), 7.07 (1H, d, $J = 8.4$ Hz, ArH), 7.01 (1H, m, ArH), 6.90 (1H, d, $J = 8.9$ Hz, ArH), 3.76 (3H, s, NCH_3). ^{13}C NMR: δ 161.06 (CONH), 137.72 (s), 136.81 (s), 128.73, 128.44 (s), 128.25 (s), 126.58 (s), 126.11, 123.76, 121.27, 119.71 (s), 118.80, 111.16 (C-7), 30.53 (NCH_3).

Analysis calculated for $\text{C}_{32}\text{H}_{24}\text{Cl}_2\text{N}_4\text{O}_2\text{S}_2$ requires:

C, 60.8; H, 3.8; N, 8.9; S, 10.2%.

Found: C, 60.6; H, 4.0; N, 8.9; S, 10.2%.

NaBH_4 (14 mg, 0.38 mmol) was added to a stirred suspension of the above compound (0.12 g, 0.19 mmol) in MeOH (5 mL). After 15 minutes, the solution was concentrated to dryness and the residue was partitioned between EtOAc and water. The organic solution was worked up to give a solid which was recrystallized from degassed CHCl_3 /benzene at -5°C to give N-phenyl 5-chloro-1-methyl-2-thioxoindole-3-carboxamide (20) [IV: $R_1 = 5\text{-Cl}$, $R_2 = \text{CONHPh}$, $R_3 = \text{Me}$] as coarse needles (86% yield); mp 312-320°C (dec).

^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 12.84 (1H, s, SH), 8.09 (1H, d, $J = 2.2$ Hz, H-4), 7.70 (2H, d, $J = 8.5$ Hz, H-2', 6'), 7.27 (2H, dd, $J = 8.5, 8.2$ Hz, H-3', 5'), 7.07 (1H, d, $J = 8.4$ Hz, H-7), 6.92 (1H, t, $J = 8.2$ Hz, H-4'), 6.86 (1H, dd, $J = 8.4, 2.2$ Hz, H-6), 3.64 (3H, s, N-CH_3).

-107-

^{13}C NMR: δ 164.73 (CONH), 140.81 (s), 135.17 (s), 130.29 (s), 128.55 (d), 123.93 (s), 121.01 (d), 118.20 (d), 117.65 (d), 117.30 (d), 107.97 (d), 104.40 (s), 29.18 (N-CH₃).

5 Analysis calculated for C₁₆H₁₃ClN₂O₂S requires:

M+ 318.0408, 316.0437.

Found: M+ (mass spectrum) 318.0414, 316.0431.

Compound 74 of Table 1

10 Similarly was prepared, from 7-chloro-1-methyl-2-indolinethione [IX: R₁ = 7-Cl, R₃ = Me];
mp 126-128°C (Inoue S, Uematsu T, Kato T, Ueda K, Pestic. Sci. 1985;16:589-598 records mp 125-127°C) and
15 phenyl isocyanate, bis[N-phenyl-7-chloro-1-methylindolyl-3-carboxamide-(2)]disulfide
[V: R₁ = 7-Cl, R₂ = CONHPh, R₃ = Me] (74) (27% yield);
mp 232-234°C.

^1H NMR (CDCl₃): δ 8.15 (1H, br, CONH), 7.85 (1H, d, J = 8.0 Hz, H-4), 7.19-7.05 (5H, m, ArH), 7.00 (1H, t, J = 6.6 Hz, ArH), 6.90 (1H, t, J = 7.8 Hz, ArH), 4.25 (3H, s, N-CH₃).

20 Analysis calculated for C₃₂H₂₄Cl₂N₄O₂S₂ requires:

C, 60.8; H, 3.8; N, 8.9%.

Found: C, 60.4; H, 4.0; N, 8.8%.

25

Compound 75 of Table 1

1,4-Dimethyl-2-indolinethione [IX: R₁ = 4-Me, R₃ = Me] (81%); mp 160-162°C.

Analysis calculated for C₁₀H₁₁NS requires:

30 C, 67.8; H, 6.3; N, 7.9; S, 18.1%

Found: C, 68.0; H, 6.4; N, 8.0; S, 18.3%

was prepared by the method given for Compound 77 (below).

-108-

Reaction of this with phenyl isocyanate gave bis[N-phenyl 1,4-dimethylindolyl-3-carboxamide-(2)]disulfide [V: $R_1 = 4\text{-CH}_3$, $R_2 = \text{CONHPh}$, $R_3 = \text{Me}$] (75); mp 237-239°C.

5 ^1H NMR (CDCl_3): δ 8.30 (1H, br s, CONH), 7.14 (1H, dd, $J = 7.3, 7.3$ hz, H-6), 7.04-6.86 (7H, m, H-5,7 and CONHPh), 3.69 (3H, s, NCH_3), 2.47 (3H, s, 4- CH_3).

10 ^{13}C NMR (CDCl_3): δ 164.57 (CONHPh), 138.59, 137.62, 131.51 (3xs), 128.62 (d), 127.23 (s), 125.11 (d), 124.15 (s), 123.94, 122.62 (2xd), 122.10 (s), 119.61, 107.91 (2xs), 30.26 (NCH_3), 19.66 (4- CH_3).

Analysis calculated for $\text{C}_{34}\text{H}_{30}\text{N}_4\text{O}_2\text{S}_2$ requires:

C, 69.1; H, 5.1; N, 9.5; S, 10.9%.

Found: C, 69.1; H, 5.1; N, 9.7; S, 11.0%.

15

Compound 76 of Table 1

1,5-Dimethyl-2-indolinethione [IX: $R_1 = 5\text{-Me}$, $R_3 = \text{Me}$]; mp 143-145°C (Bull. Fr. 1987:181 reports mp 132-133°C) was prepared by the method given for Compound 77 (below). Reaction of this with phenyl isocyanate gave bis[N-phenyl 1,5-dimethylindolyl-3-carboxamide-(2)]disulfide [V: $R_1 = 5\text{-CH}_3$, $R_2 = \text{CONHPh}$, $R_3 = \text{Me}$] (76); mp 231-234°C.

20 ^1H NMR (CDCl_3): δ 8.24 (1H, br s, CONH), 7.78 (1H, br, H-4), 7.19-7.13 (4H, m, CONHPh), 7.05-6.90 (3H, m, H-6,7 and CONHPh), 3.71 (3H, s, NCH_3), 2.36 (3H, s, 5- CH_3).

25 ^{13}C NMR (CDCl_3): δ 161.75 (CONH), 138.00, 137.10, 131.77, 129.01 (4xs), 128.53, 127.37 (2xd), 126.35 (s), 123.40, 121.33, 119.85, 109.85 (4xd), 30.32 (NCH_3), 21.57 (5- CH_3).

30 Analysis calculated for $\text{C}_{34}\text{H}_{30}\text{N}_4\text{O}_2\text{S}_2$ requires:

C, 69.1; H, 5.1; N, 9.5; S, 10.9%.

Found: C, 69.4; H, 5.2; N, 9.6; S, 11.2%.

-109-

Compound 77 of Table 1

A mixture of 2,5-dimethylaniline (27.4 g, 0.2 mol) and benzotriazole (23.8 g, 0.2 mol) in EtOH (300 mL) was stirred at 20°C as 37% aqueous formaldehyde (16.1 g, 0.2 mol) was added gradually. After 30 minutes, the white solid which precipitated was collected and washed with EtOH to give N-(1-benzotriazolylmethyl)-2,5-dimethylaniline (33.9 g, 67% yield); mp (EtOH) 147-149°C.

¹H NMR (CDCl₃): δ 6.85-8.10 (7H, m, ArH), 6.56 (minor isomer) and 6.13 (major isomer) (2H, 2xm, CH₂), 5.08 (minor) and 4.70 (major) (1H, 2xm, NH), 2.24 (3H, s, CH₃), and 2.12 (3H, s, CH₃).

Analysis calculated for C₁₅H₁₆N₄ requires:

C, 70.6; H, 5.9; N, 23.5%.

Found: C, 71.5; H, 6.3; N, 22.1%.

A suspension of this compound (33 g, 0.13 mol) and NaBH₄ (5 g) in dioxane (400 mL) was heated under reflux for 5 hours, and the solution was concentrated. After cooling, water was added and the resulting mixture was extracted with EtOAc. The organic layer was washed twice with aqueous K₂CO₃ and water, and dried (Na₂SO₄). Removal of the solvent gave N,2,5-trimethylaniline (17.6 g, 99% yield) as an oil, which was used directly.

¹H NMR (CDCl₃): δ 6.93 (1H, d, J = 7.4 Hz, H-3), 6.49 (1H, d, J = 7.6 Hz, H-4), 6.44 (1H, s, H-6), 3.72, (1H, s, NH), 2.88 (3H, s, NCH₃), 2.31 (3H, s, CH₃), and 2.09 (3H, s, CH₃).

A solution of 2,4,6-trimethylaniline (6.86 g, 5 mmol) in dry THF (100 mL) under an atmosphere of N₂ was cooled to -78°C and n-butyllithium (21 mL, 2.5 M solution in hexanes) was added dropwise. The mixture was allowed to warm to 0°C, and dry CO₂ gas was bubbled in for 2-3 minutes. The excess CO₂ was removed under

-110-

vacuum, and after the addition of further THF to replace that lost by evaporation, the solution was recooled to -78°C . n-Butyllithium (22 mL, 2.5 M solution in hexanes) was again added dropwise, and the temperature was then allowed to rise slowly to -10°C where a deep red colored solution was obtained. After a further 30 minutes at that temperature, the mixture was again recooled to -78°C and CO_2 gas was bubbled in until the red color disappeared. The reaction mixture was allowed to warm to 20°C , and after removal of the solvent, 0.1 M HCL (50 mL) was added to initiate both deprotection of the nitrogen and ring-closure. The resulting mixture was extracted with EtOAc, and this was then washed successively with 0.1 M HCL, water, and dilute aqueous Na_2CO_3 . After drying (Na_2SO_4), the solvent was removed under vacuum, to leave an oil which was purified by chromatography on Al_2O_3 to give 1,6-dimethyl-2-indolinone (3.37 g, 42% yield)

[VII: $\text{R}_1 = 6\text{-Me}$; $\text{R}_3 = \text{Me}$]; mp (hexane) $94.5\text{-}96^{\circ}\text{C}$.

^1H NMR (CDCl_3): δ 7.11 (2H, d, $J = 7.5$ Hz, H-4), 6.85 (2H, d, $J = 7.5$ Hz, H-5), 6.65 (1H, s, H-7), 3.47 (2H, s, CH_2), 3.19 (3H, s, 1- CH_3), and 2.38 (3H, s, 6- CH_3).

Analysis calculated for $\text{C}_{10}\text{H}_{11}\text{NO}$ requires:

C, 74.5; H, 6.9; N, 8.7%.

Found: C, 74.5; H, 6.6; N, 8.7%.

Thiation of this with P_2S_5 as above gave 1,6-dimethyl-2-indolinethione [IX: $\text{R}_1 = 6\text{-Me}$, $\text{R}_3 = \text{Me}$]; mp $141\text{-}143^{\circ}\text{C}$.

Analysis calculated for $\text{C}_{10}\text{H}_{11}\text{NS}$ requires:

C, 67.8; H, 6.3; N, 7.9; S, 18.1%.

Found: C, 67.6; H, 6.5; N, 8.2; S, 18.0%.

-111-

This was reacted with phenyl isocyanate as above to give bis[N-phenyl 1,6-dimethylindolyl-3-carboxamide-(2)]disulfide [V: $R_1 = 6\text{-CH}_3$, $R_2 = \text{CONHPh}$, $R_3 = \text{Me}$] (77); mp 192-195°C.

- 5 ^1H NMR (CDCl_3): δ 8.16 (1H, br s, CONH), 7.85 (1H, d, $J = 8.3$ Hz, H-4), 7.10 (4H, br, CONHPh), 6.98 (1H, m, CONHPh), 6.87 (1H, d, $J = 8.3$ Hz, H-5), 6.73 (1H, br, H-7), 3.71 (3H, s, NCH_3), 2.35 (3H, s, 6-CH_3).
- 10 ^{13}C NMR (CDCl_3): δ 161.49 (CONH), 139.05, 137.98, 135.63 (3xs), 128.44 (d), 126.10 (s), 124.28 (d), 124.06 (s), 123.17, 121.61, 119.21, 109.85 (4xd), 30.17 (NCH_3), 21.98 (6-CH_3).

Analysis calculated for $\text{C}_{34}\text{H}_{30}\text{N}_4\text{O}_2\text{S}_2$ requires:

- C, 69.1; H, 5.1; N, 9.5; S, 10.9%.
- 15 Found: C, 68.9; H, 5.2; N, 9.6; S, 11.0%.

Compound 78 of Table 1

Similarly was prepared 1,7-dimethyl-2-indolinethione [IX: $R_1 = 7\text{-Me}$, $R_3 = \text{Me}$]; mp 138-9°C.

- 20 Analysis calculated for $\text{C}_{10}\text{H}_{11}\text{NS}$ requires:

C, 67.8; H, 6.3; N, 7.9; S, 18.1%.

Found: C, 67.6; H, 6.2; N, 8.0; S, 18.1%.

Reaction of this with phenyl isocyanate gave bis[N-phenyl 1,7-dimethylindolyl-3-carboxamide-(2)]-disulfide [V: $R_1 = 7\text{-CH}_3$, $R_2 = \text{CONHPh}$, $R_3 = \text{Me}$] (78); mp 221-223°C.

- 25 ^1H NMR (CDCl_3): δ 8.11 (1H, br s, CONH), 7.83 (1H, $J = 8.1$ Hz, H-4), 7.15-7.07 (4H, m, CONHPh), 6.99 (1H, m, CONHPh), 6.94 (1H, dd, $J = 8.1$, 8.1 Hz, H-5), 6.85 (1H, d, $J = 8.1$ Hz, H-6), 4.07 (3H, s, NCH_3), 2.44 (3H, s, 7-CH_3).
- 30 ^{13}C NMR (CDCl_3): δ 161.67 (CONH), 137.95, 137.86 (2xs), 128.55, 128.31 (2xd), 126.85 (s), 123.57, 122.10

-112-

(2xd), 121.77 (s), 119.72, 119.21 (2xd), 33.36 (NCH₃), 20.23 (7-CH₃).

Analysis calculated for C₃₄H₃₀N₄O₂S₂ requires:

C, 69.1; H, 5.1; N, 9.5; S, 10.9%.

5 Found: C, 69.1; H, 5.2; N, 9.7; S, 11.0%.

Compound 79 of Table 1

Similarly was prepared, from 4-methoxy-1-methyl-2-indolinethione [IX: R₁ = 4-OMe, R₃ = Me];
10 mp 141-144°C (US Patent 5,030,646 records mp 126-128°C)
and phenyl isocyanate, bis[N-phenyl 4-methoxy-1-methylindolyl-3-carboxamide-(2)]disulfide
[V: R₁ = 4-OCH₃, R₂ = CONHPh, R₃ = Me] (79);
mp 225-228°C.

15 ¹H NMR (CDCl₃): δ 8.85 (1H, br s, CONH), 7.25-7.06 (5H, m, H-6 and CONHPh), 6.98 (1H, m, CONHPh), 6.82 (1H, d, J = 8.3 Hz, H-7), 6.36 (1H, d, J = 7.8 Hz, H-5), 3.76 (3H, s, OCH₃), 3.69 (3H, s, NCH₃).

¹³C NMR (CDCl₃): 162.36 (CONH), 152.70, 139.39,
20 138.73, 130.20 (4xs), 128.54, 125.39, 123.08 (3xs), 130.20 (s), 128.54, 125.39, 123.08 (3xd), 19.96 (s), 119.19 (d), 114.66 (s), 103.67, 101.55 (2xd), 22.58 (OCH₃), 30.48 (NCH₃).

Analysis calculated for C₃₄H₃₀N₄O₄S₂ requires:

25 C, 65.6; H, 4.9; N, 9.0; S, 10.3%.

Found: C, 65.7; H, 4.9; N, 9.2; S, 10.2%.

Compound 80 of Table 1

Similarly was prepared, from 5-methoxy-1-methyl-2-indolinethione [IX: R₁ = 5-OMe, R₃ = Me];
30 mp 148-150°C (US Patent 5,030,646 records mp 142-144°C)
and phenyl isocyanate, bis[N-phenyl 5-methoxy-1-methylindolyl-3-carboxamide-(2)]disulfide

-113-

[V: $R_1 = 5\text{-OCH}_3$, $R_2 = \text{CONHPh}$, $R_3 = \text{Me}$] (80);

mp 161-164°C.

^1H NMR (CDCl_3): δ 8.41 (1H, br s, CONH), 7.55 (d, $J = 1.8$ Hz, H-4), 7.18 (4H, m, CONHPh), 7.00 (2H, m, H-6 and CONHPh), 6.89 (1H, d, $J = 7.4$ Hz, H-7), 3.82 (3H, s, OCH_3), 3.68 (3H, s, NCH_3).

^{13}C NMR (CDCl_3): δ 161.80 (CONH), 155.94, 137.87, 134.07 (3xs), 128.71, 123.68, 119.50, 117.48, 111.10, 102.29 (6xd), 55.63 (OCH_3), 30.47 (NCH_3).

Analysis calculated for $\text{C}_{34}\text{H}_{30}\text{N}_4\text{O}_4\text{S}_2$ requires:

C, 65.6; H, 4.9; N, 9.0; S, 10.3%.

Found: C, 65.3; H, 5.1; N, 9.2; S, 10.4%.

Compound 81 of Table 1

Similarly was prepared, from 6-methoxy-1-methyl-2-indolinethione [IX: $R_1 = 6\text{-OMe}$, $R_3 = \text{Me}$]; mp 133-136°C (US Patent 5,030,646 records mp 135-136°C) and phenyl isocyanate, bis[N-phenyl 6-methoxy-1-methylindolyl-3-carboxamide-(2)]disulfide

[V: $R_1 = 6\text{-OCH}_3$, $R_2 = \text{CONHPh}$, $R_3 = \text{Me}$] (81);

mp 197-200°C.

^1H NMR (CDCl_3): δ 8.19 (1H, br s, CONH), 7.91 (1H, d, $J = 8.9$ Hz, H-4), 7.12 (4H, br, CONHPh), 6.97 (1H, m, CONHPh), 6.71 (1H, d, $J = 8.9$ Hz, H-5), 6.25 (1H, br, H-7), 3.74 (3H, s, OCH_3), 3.70 (3H, s, NCH_3).

^{13}C NMR (CDCl_3): δ 161.37 (CONH), 158.75, 139.82, 138.04, 128.65 (4xs), 128.50, 123.30, 123.12, (3xd), 120.64, 120.26 (2xs), 119.10, 113.22, 98.02 (3xd), 55.26 (OCH_3), 30.21 (NCH_3).

Analysis calculated for $\text{C}_{34}\text{H}_{30}\text{N}_4\text{O}_4\text{S}_2$ requires:

C, 65.6; H, 4.9; N, 9.0; S, 10.3%.

Found: C, 65.5; H, 4.8; N, 9.2; S, 10.4%.

-114-

Compound 82 of Table 1

Similarly was prepared, from 7-methoxy-1-methyl-2-indolinethione [IX: $R_1 = 7\text{-OMe}$, $R_3 = \text{Me}$]; mp 124-126°C (US Patent 5,030,646 records mp 114-116°C) and phenyl isocyanate, bis[N-phenyl 7-methoxy-1-methylindolyl-3-carboxamide-(2)]disulfide [V: $R_1 = 7\text{-OCH}_3$, $R_2 = \text{CONHPh}$, $R_3 = \text{Me}$] (82); mp 205-208°C.

^1H NMR (CDCl_3): δ 8.14 (1H, br s, CONH), 7.57 (1H, d, $J = 8.2$ Hz, H-4), 7.13 (4H, m, CONHPh), 6.96 (1H, m, CPNHPh), 6.93 (1H, dd, $J = 8.2$, 8.2 Hz, H-5), 6.48 (1H, d, $J = 8.2$ Hz, H-6), 4.12 (3H, s, OCH_3), 3.73 (3H, s, NCH_3).

^{13}C NMR (CDCl_3): δ 161.72 (CONH), 147.12, 137.99, 129.08 (3xs), 128.45 (d), 128.01 (s), 123.27, 122.35, 119.33, 114.13, 105.35 (5xd), 55.22 (OCH_3), 33.73 (NCH_3).

Analysis calculated for $\text{C}_{34}\text{H}_{30}\text{N}_4\text{O}_4\text{S}_2$ requires:

C, 65.6; H, 4.9; N, 9.0; S, 10.3%.

Found: C, 64.9; H, 5.0; N, 9.0; S, 10.4%.

Compound 84 of Table 1

A solution of 3-(methylthio)-5-(trifluoromethyl)-oxindole (Gassman PG, Cue BW, Luh T-Y, J. Org. Chem. 1977;42:1344-1348) (10 g, 40 mmol) in AcOH (100 mL) was heated under reflux with Zn dust (13.3 g, 0.2 mol) for 1 hour. The mixture was cooled and filtered, and the precipitate was washed with AcOH. The combined filtrates were evaporated under reduced pressure, and the residue was diluted with 1 M aqueous ammonia to give 5-trifluoromethyloxindole [VII: $R_1 = 5\text{-CF}_3$, $R_3 = \text{H}$] (7.22 g, 90%); mp (aqueous EtOH) 188.5-191°C (lit. [Hardtmann GE, USP 4,160,032; Chem. Abstr. 1979;91:P107890w]; mp 188-189°C).

-115-

^1H NMR (CDCl_3): δ 8.74 (1H, s, NH), 7.52 (1H, d, J = 8.2 Hz, H-6), 7.49 (1H, s, H-4), 6.97 (1H, d, J = 8.2 Hz, H-7), 3.61 (2H, s, CH_2).

A suspension of the above oxindole (5.03 g, 25 mmol) in water (100 mL) containing NaOH (1.5 g) was treated with Me_2SO_4 (4.7 g, 37 mmol). The mixture was warmed to 100°C for 10 minutes, cooled, a further portion of Me_2SO_4 and NaOH added, and warmed again briefly. After thorough cooling, the solid was collected and chromatographed on alumina. Elution with CH_2Cl_2 /hexane (7:3) gave 1-methyl-5-(trifluoromethyl)-oxindole [VII: R_1 = 5- CF_3 , R_3 = Me] (3.5 g, 65%); mp (hexane) 127.5-129°C.

^1H NMR (CDCl_3): δ 7.58 (1H, d, J = 8.2 Hz, H-6), 7.50 (1H, s, H-4), 6.89 (1H, d, J = 8.2 Hz, H-7), 3.58 (2H, s, CH_2), 3.25 (3H, s, CH_3).

Analysis calculated for $\text{C}_{10}\text{H}_8\text{F}_3\text{NO}$ requires:

C, 55.8; H, 3.8; N, 6.5%.

Found: C, 55.5; H, 3.8; N, 6.5%.

Reaction of this compound with P_2S_5 as above gave 1-methyl-5-(trifluoromethyl)-2-indolinethione [IX: R_1 = 5- CF_3 , R_3 = Me] (96% yield); mp 124.5-126°C. ^1H NMR (CDCl_3): δ 7.63 (1H, dd, J = 8.3, 0.8 Hz, H-6), 7.54 (1H, d, J = 0.8 Hz, H-4), 7.03 (1H, d, J = 8.3 Hz, H-7), 4.15 (2H, s, C-3), 3.64 (3H, s, N- CH_3).

^{13}C NMR: δ 202.28 (C-2), 149.34 (s), 129.60 (s), 126.54 (J = 32.5 Hz, C-5), 125.9 (J = 4.0 Hz), 124.21 (J = 271.9 Hz) (CF_3), 121.00 (J = 3.8 Hz), 109.28 (d), 48.75 (C-3), 31.35 (N- CH_3).

Analysis calculated for $(\text{C}_{10}\text{H}_8\text{F}_3\text{NS})$ requires:

C, 51.9; H, 3.5; N, 6.3; S, 14.1%.

Found: C, 52.0; H, 3.7; N, 6.3; S, 14.1%.

Reaction of this with phenyl isocyanate as above gave 2,2-dithiobis[N-phenyl-1-methyl-5-(trifluoro-

-116-

methyl)indolyl-3-carboxamide] (84) [V: $R_1 = 5\text{-CF}_3$,
 $R_2 = \text{CONHPh}$, $R_3 = \text{Me}$] (71% yield); mp 214-216°C.

^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 9.53 (1H, s, CONH), 8.14 (1H, br s, H-4), 7.59 (1H, d, $J = 8.8$ Hz, H-7), 7.53 (1H, dd, $J = 8.8$, 1.5 Hz, H-6), 7.12-7.09 (4H, m, ArH), 6.97 (1H, m, ArH), 3.76 (3H, s, N-CH₃).

^{13}C NMR: δ 160.49 (CONH), 138.93 (s), 138.21 (s), 131.76 (s), 128.19 (d), 124.96 ($J = 271.6$ Hz, CF₃), 124.60 (d), 119.21 (s), 119.09 (d), 118.57 ($J = 4.1$ Hz), 30.46 (N-CH₃).

Analysis calculated for C₃₄H₂₄F₆N₄O₂S₂ requires:

C, 58.4; H, 3.5; N, 8.0; S, 9.2%.

Found: C, 58.5; H, 3.8; N, 7.9; S, 9.3%.

Compound 85 of Table 1

Methylation of 6-chlorooxindole [VII: $R_1 = 6\text{-Cl}$, $R_3 = \text{H}$] (Quallich GJ, Morrissey PM, Synthesis 1993:51-53) with Me₂SO₄/NaOH as above gave 6-chloro-1-methyloxindole [VII: $R_1 = 6\text{-Cl}$, $R_3 = \text{CH}_3$];

mp (aqueous EtOH) 119.5-122°C.

^1H NMR (CDCl₃): δ 7.15 (1H, d, $J = 7.8$ Hz, H-4), 7.01 (1H, dd, $J = 7.8$, 1.8 Hz, H-5), 6.82 (1H, d, $J = 1.7$ Hz, H-7), 3.49 (2H, s, CH₂), 3.19 (3H, s, CH₃).

Analysis calculated for C₉H₈ClNO requires:

C, 59.5; H, 4.4; N, 7.7%.

Found: C, 59.6; H, 4.6; N, 7.6%.

Reaction of this with P₂S₅ as above gave 6-chloro-1-methyl-2-indolinethione [IX: $R_1 = 6\text{-Cl}$, $R_3 = \text{Me}$] (87% yield); mp (EtOAc/petroleum ether) 162-165°C.

^1H NMR (CDCl₃): δ 7.20 (1H, d, $J = 7.9$ Hz, H-4), 7.13 (1H, dd, $J = 7.9$, 1.7 Hz, H-5), 6.96 (1H, d, $J = 1.7$ Hz, H-7), 4.06 (2H, s, H-3), 3.59 (3H, s, N-CH₃).

-117-

^{13}C NMR: δ 202.00 (C-2), 147.76 (s), 133.98 (s), 127.35 (s), 124.64 (d), 124.06 (d), 110.20 (d), 48.59 (C-3), 31.29 (N-CH₃).

Analysis calculated for C₉H₈ClN₂SO requires:

5 C, 54.7; H, 4.1; N, 7.1; S, 16.2%.

Found: C, 54.8; H, 4.1; N, 7.0; S, 16.3%.

Reaction of this with phenyl isocyanate as above gave bis[N-phenyl 6-chloro-1-methylindolyl-

10 3-carboxamide-(2)]disulfide (85) [V: R₁ = 6-Cl, R₂ = CONHPh, R₃ = Me] (61% yield); mp 243-245°C.

^1H NMR ((CD₃)₂SO): δ 9.43 (1H, br, CONH), 7.77 (1H, d, J = 8.6 Hz, H-4), 7.46 (1H, d, J = 1.4 Hz, H-7), 7.19-7.09 (5H, m, ArH), 7.01 (1H, m, ArH), 3.67 (3H, s, N-CH₃).

15 ^{13}C NMR: δ 160.66 (CONH), 138.29 (s), 138.04 (s), 129.87 (s), 129.41 (s), 128.15 (d), 123.94 (s), 122.91 (d), 122.37 (d), 121.70 (d), 119.20 (s), 119.12 (d), 110.69 (d), 30.22 (N-CH₃).

Analysis calculated for C₃₂H₂₄Cl₂N₄O₂S₂ requires:

20 C, 60.9; H, 3.8; N, 8.9; S, 10.2%.

Found: C, 60.9; H, 4.0; N, 8.7; S, 10.2%.

Compound 86 of Table 1

25 Similarly was prepared, from 1-methyl-5-nitro-2-oxindole (Robinson R, Wyler M, J. Chem. Soc. 1941:620-624), 1-methyl-5-nitro-2-indolinethione [IX: R₁ = 5-NO₂, R₃ = Me] (68% yield); mp (EtOAc/light petroleum) >330°C.

30 ^1H NMR ((CD₃)₂SO): δ 8.28 (1H, dd, J = 8.7, 1.7 Hz, H-6), 8.17 (1H, d, J = 1.7 Hz, H-4), 7.41 (1H, d, J = 8.7 Hz, H-7), 4.26 (2H, s, H-3), 3.60 (3H, s, N-CH₃).

-118-

^{13}C NMR: δ 203.48 (C-2), 151.49 (s), 143.81 (s), 130.53 (s), 124.80 (d), 119.00 (d), 110.24 (d), 48.45 (C-3), 31.34 (N-CH₃).

Analysis calculated for C₉H₈N₂SO₂ requires:

5 M+ 208.0306.

Found: M+ 208.0311 (mass spectrum).

Reaction of this with phenyl isocyanate as above gave 2,2'-dithiobis[N-phenyl-1-methyl-5-nitroindolyl-3-carboxamide] (86) [V: R₁ = 5-NO₂, R₂ = CONHPh, R₃ = Me] (52% yield); mp 236-240°C (dec).

10 ^1H NMR ((CD₃)₂CO): δ 9.68 (1H, br, CONH), 8.64 (1H, d, J = 1.6 Hz, H, H-4), 8.07 (1H, dd, J = 8.8, 1.6 Hz, H-6), 7.56 (1H, d, J = 8.8 Hz, H-7), 7.18-7.08 (4H, m, ArH), 6.98 (1H, t, J = 6.8 Hz, ArH), 3.79 (3H, s, N-CH₃).

15 ^{13}C NMR: δ 160.04 (CONH) 141.96 (s), 140.17 (s), 138.22 (s), 128.24 (d), 124.35 (s), 123.09 (d), 120.25 (s), 118.90 (d), 117.76 (d), 111.64 (d), 30.70 (N-CH₃).

Analysis calculated for C₃₂H₂₄N₆O₆S₂·0.2H₂O requires:

20 C, 55.8; H, 4.1; N, 12.2%.

Found: C, 55.5; H, 3.9; N, 12.0%.

Analysis calculated for C₃₂H₂₅N₆S₂O₆ requires:

[M + H]⁺ 653.1277.

Found: [M + H]⁺ 653.1275 (FAB mass spectrum).

25

Compound 87 of Table 1

Similarly was prepared, from 5-fluoro-1-methyloxindole (Wiseman EH, Chiaini J, McManus JM, J. Med. Chem. 1973;16:131-134), 5-fluoro-1-methyl-2-indolinethione [IX: R₁ = 5-F, R₃ = Me] (93% yield); mp 155-157°C.

30 ^1H NMR (CDCl₃): δ 7.11-6.99 (2H, m, H-4,6), 6.88 (1H, dd, J = 9.3, 4.2 Hz, H-7), 4.09 (2H, s, H-3), 3.61 (3H, s, N-CH₃).

-119-

¹³C NMR: δ 200.61 (C-2), 160.49 (J = 243.6 Hz, C-5), 142.76 (s), 130.80 (J = 8.6 Hz, C-3a), 114.48 (J = 24.1 Hz), 112.13 (J = 25.1 Hz), 109.94 (J = 8.6 Hz), 48.96 (J = 1.8 Hz, C-3), 31.38 (N-CH₃).

5 Analysis calculated for C₉H₈FNS requires:

C, 59.7; H, 4.5; N, 7.7; S, 17.7%.

Found: C, 59.7; H, 4.6; N, 7.8; S, 17.4%.

Reaction of this with phenyl isocyanate as above gave 2,2'-dithiobis[N-phenyl-5-fluoro-

10 1-methylindolyl-3-carboxamide] (87) [V: R₁ = 5-F, R₂ = CONHPh, R₃ = Me] (74% yield); mp 205-207°C.

¹H NMR (CDCl₃): δ 8.17 (1H, br, CONH), 7.64 (1H, dd, J = 9.4, 2.0 Hz, H-4), 7.17 (4H, br d, ArH), 7.00 (1H, m, ArH), 6.95-6.88 (2H, m, ArH), 3.78 (3H, s, N-CH₃).

15 ¹³C NMR: δ 161.17 (CONH), 158.97 (J = 239.4 Hz, C-5), 138.02 (s), 135.71 (s), 128.69 (d), 123.69 (d), 118.87 (d), 114.66 (J = 27.1 Hz), 111.14 (J = 10.0 Hz), 106.92 (J = 25.5 Hz), 30.61 (N-CH₃).

Analysis calculated for C₃₂H₂₄F₂N₄O₂S₂ requires:

20 C, 64.2; H, 4.0; N, 9.4; S, 10.7%.

Found: C, 63.9; H, 4.2; N, 9.3; S, 10.7%.

Compound 88 of Table 1

Reduction of 5-cyano-3-methylthiooxindole

25 (Gassman PG, Cue BW, Luh T-Y, J. Org. Chem. 1977;42:1344-1348) with Zn/AcOH as above gave 5-cyanooxindole [VII: R₁ = 5-CN; R₃ = H] (89% yield); mp (aqueous EtOH) 249°C (dec) (lit. [Gassman PG, Gilbert DP, Luh T-Y, JOC 1977;42:1340-1344];

30 mp 249-251°C). Methylation of this with Me₂SO₄/NaOH as above gave 5-cyano-1-methyloxindole [VII: R₁ = 5-CN, R₃ = H] (53% yield); mp (hexane) 201-203°C.

-120-

^1H NMR (CDCl_3): δ 7.63 (1H, dd, J = 8.1, 1.1 Hz, H-6), 7.51 (1H, d, J = 1.1 Hz, H-4), 6.90 (1H, d, J = 8.1 Hz, H-7), 3.57 (2H, s, CH_2), 3.25 (3H, s, CH_3).

Analysis calculated for $\text{C}_{10}\text{H}_8\text{N}_2\text{O}$ requires:

5 C, 69.8; H, 4.7; N, 16.3%.

Found: C, 70.2; H, 4.64; N, 16.7%.

Reaction of the above compound with P_2S_5 gave 5-cyano-1-methyl-2-indolinethione [IX: R_1 = 5-CN, R_3 = Me] (41% yield); mp 185-187°C.

10 ^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 7.87 (1H, br d, J = 8.3 Hz, H-6), 7.76 (1H, br s, H-4), 7.41 (1H, d, J = 8.3 Hz, H-7), 4.22 (2H, s, H-3), 3.58 (3H, s, N- CH_3).

15 ^{13}C NMR: δ 202.34 (C-2), 149.78 (s), 133.05 (d), 130.42 (s), 126.92 (d), 119.05 (s), 110.98 (d), 48.20 (C-3), 31.11 (N- CH_3).

Analysis calculated for $\text{C}_{10}\text{H}_8\text{N}_2\text{S} \cdot 0.5\text{H}_2\text{O}$ requires:

C, 60.7; H, 4.6; N, 14.2%.

Found: C, 61.3; H, 4.1; N, 14.4%.

20 Reaction of this with phenyl isocyanate as above gave 2,2'-dithiobis[N-phenyl-5-cyano-1-methylindolyl-3-carboxamide] (88) [V: R_1 = 5-CN, R_2 = CONHPh, R_3 = Me] (47% yield); mp 221-224°C.

25 ^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 9.51 (1H, s, CONH), 8.18 (1H, br s, H-4), 7.60-7.48 (2H, m, H-6,7), 7.20-7.06 (4H, m, ArH), 7.00 (1H, br s, ArH), 3.75 (3H, s, N- CH_3).

^{13}C NMR: δ 160.21 (CONH), 138.97 (s), 138.26 (s), 132.74 (C-5), 128.77 (s), 128.27 (d), 126.52 (d), 124.72 (s), 123.14 (d), 119.80 (s), 119.11 (d), 118.87 (s), 112.29 (d), 103.53 (CN), 30.46 (N- CH_3).

30 Analysis calculated for $\text{C}_{34}\text{H}_{24}\text{N}_6\text{O}_2\text{S}_2 \cdot 0.5\text{H}_2\text{O}$ requires:

C, 65.7; H, 4.1; N, 13.5; S, 10.3%.

Found: C, 65.6; H, 4.0; N, 13.5; S, 10.6%.

-121-

Compound 89 of Table 1

Similarly was prepared, from 5-bromo-1-methyl-2-indolinethione [IX: $R_1 = 5\text{-Br}$, $R_3 = \text{Me}$]; mp 137-139°C, (Baudin J-B, Julia SA, Lorne R, Bull. Soc. Chim. France 1987:181 records mp 126-127°C) and phenyl isocyanate as above, 2,2'-dithiobis[N-phenyl-5-bromo-1-methylindolyl-3-carboxamide] (89)

[V: $R_1 = 5\text{-Br}$, $R_2 = \text{CONHPh}$, $R_3 = \text{Me}$] (68% yield); mp 219-221°C.

^1H NMR (CDCl_3): δ 8.14 (1H, br, CONH), 8.10 (1H, d, $J = 1.6$ Hz, H-4), 7.21-7.12 (5H, m, ArH), 7.01 (1H, m, ArH), 6.83 (1H, br d, $J = 8.2$ Hz, ArH), 3.73 (3H, s, N-CH₃).

^{13}C NMR: δ 161.04 (CONH), 137.68 (s), 137.00 (s), 128.75 (d), 128.60 (d), 127.13 (s), 124.29 (d), 123.78 (d), 118.82 (d), 115.92 (s), 111.46 (d), 30.48 (N-CH₃).

Analysis calculated for $\text{C}_{32}\text{H}_{24}\text{Br}_2\text{N}_4\text{O}_2\text{S}_2$ requires:

C, 53.3; H, 3.4; N, 7.8; S, 8.9%.

Found: C, 53.1; H, 3.5; N, 7.7; S, 8.9%.

Compound 90 of Table 1

A solution of 4-methoxy-1-methyl-2-oxindole [VII: $R_1 = 4\text{-OMe}$, $R_3 = \text{Me}$] (1.20 g, 6.77 mmol) in 48% HBr/glacial AcOH (40 mL) was heated under reflux for 6 hours, then poured into water. The precipitate of crude phenol was filtered off, washed well with water and dried, then acetylated with Ac₂O/pyridine for 1 hour at 20°C. Solvents were removed under reduced pressure, and the residue was partitioned between EtOAc and 3N HCl. Chromatography of the organic residue on silica gel, eluting with EtOAc/petroleum ether gave 4-acetoxy-1-methyl-2-oxindole [VII: $R_1 = 4\text{-OAc}$, $R_3 = \text{Me}$] (75% yield); mp 109-111°C.

-122-

^1H NMR (CDCl_3): δ 7.30 (1H, dd, $J = 8.2, 7.7$ Hz, H-6), 6.78 (1H, d, $J = 8.2$ Hz, H-7), 6.71 (1H, d, $J = 7.7$ Hz, H-5), 3.41 (2H, s, H-3), 3.22 (3H, s, N-CH₃), 2.32 (3H, s, OCOCH₃).

5 ^{13}C NMR: δ 174.26 (C-2), 168.30 (OCOCH₃), 164.71 (s), 146.58 (s), 129.12, 116.62 (s), 115.83 (d), 105.90 (d), 33.74 (C-3), 26.51 (N-CH₃), 20.83 (COOCH₃).

Analysis calculated for $\text{C}_{11}\text{H}_{11}\text{NO}_3$ requires:

C, 64.4; H, 5.4; N, 6.8%.

10 Found: C, 64.3; H, 5.4; N, 7.0%.

Reaction of this with P_2S_5 as above gave

4-acetoxy-1-methyl-2-indolinethione [IX: $\text{R}_1 = 4\text{-OAc}$, $\text{R}_3 = \text{Me}$] (94% yield); mp 156°C.

15 ^1H NMR (CDCl_3): δ 7.35 (1H, dd, $J = 8.2, 7.9$ Hz, H-6), 6.90 (1H, d, $J = 8.2$ Hz, H-7), 6.86 (1H, d, $J = 7.9$ Hz, H-5), 4.00 (2H, s, H-3), 3.61 (3H, s, N-CH₃), 2.32 (3H, s, OCOCH₃).

20 ^{13}C NMR: δ 200.75 (C-2), 168.14 (OCOCH₃), 148.30 (s), 146.27 (s), 129.44 (d), 121.18 (s), 117.69 (d), 107.32 (d), 47.09 (C-3), 31.57 (N-CH₃), 20.81 (COOCH₃).

Analysis calculated for $\text{C}_{11}\text{H}_{11}\text{NO}_2\text{S}$ requires:

C, 59.7; H, 5.0; N, 6.3; S, 14.5%.

Found: C, 59.4; H, 5.2; N, 6.6; S, 14.5%.

Reaction with phenyl isocyanate as above gave

25 2,2'-dithiobis[N-phenyl 4-acetoxy-1-methylindolyl-3-carboxamide] (90) [V: $\text{R}_1 = 4\text{-OAc}$, $\text{R}_2 = \text{CONHPh}$, $\text{R}_3 = \text{Me}$] (31%); mp 194°C.

30 ^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 9.92 (1H, s, CONH), 7.34-7.27 (4H, m, H-5,7,2',6'), 7.14 (2H, dd, $J = 7.8, 7.6$ Hz, H-3',5'), 6.98 (1H, t, $J = 7.8$ Hz, H-5'), 6.89 (1H, dd, $J = 8.0, 7.8$ Hz, H-5), 3.66 (3H, s, NCH₃), 1.95 (3H, s, OCH₃).

^{13}C NMR: δ 168.57 (CONHPh), 162.09 (OCOCH₃), 142.91 (s), 139.20 (s), 138.75 (s), 129.01 (s), 128.38 (d),

-123-

124.56 (d), 123.14 (d), 119.23 (s), 118.38 (d), 117.70 (s), 113.94 (d), 108.70 (d), 30.39 (N-CH₃), 20.32 (COOCH₃).

Analysis calculated for C₃₆H₃₀N₄O₆S₂ requires:

5 679.1685.

Found: [M + H]⁺ 679.1705 (FABMS).

Compound 91 of Table 1

10 Similar demethylation/acetylation of 5-methoxy-1-methyl-2-oxindole [VII: R₁ = 5-OMe, R₃ = Me] gave 5-acetoxy-1-methyl-2-oxindole [VII: R₁ = 5-OAc, R₃ = Me] (70% yield); mp (EtOAc/petroleum ether) 104-106°C.

15 ¹H NMR (CDCl₃): δ 7.01 (1H, br s, H-4), 7.00 (1H, dd, J = 9.1, 2.4 Hz, H-6), 3.53 (2H, s, H-3), 3.20 (3H, s, N-CH₃), 2.30 (3H, s, OCOCH₃).

¹³C NMR: δ 174.79 (C-2), 169.96 (OCOCH₃), 146.08 (s), 142.96 (s), 125.50 (s), 120.84 (d), 118.54 (d), 108.25 (d), 35.89 (C-3), 26.30 (N-CH₃), 21.04 (OCOCH₃).

20 Analysis calculated for C₁₁H₁₁NO₃ requires:

C, 64.4; H, 5.4; N, 6.8%.

Found: C, 64.4; H, 5.4; N, 6.8%.

25 Reaction of this with P₂S₅ as above gave 5-acetoxy-1-methyl-2-indolinethione [IX: R₁ = 5-OAc, R₃ = Me] (86% yield); mp 134-135.5°C.

¹H NMR (CDCl₃): δ 7.06 (2H, br s, H-4,6), 6.93 (1H, d, J = 8.6 Hz, H-7), 4.08 (2H, s, H-3), 3.60 (3H, s, N-CH₃), 2.31 (3H, s, OCOCH₃).

30 ¹³C NMR: δ 200.86 (C-2), 169.62 (OCOCH₃), 147.62 (s), 144.14 (s), 130.10 (s), 120.97 (d), 117.99 (d), 109.62 (d), 48.79 (C-3), 31.24 (N-CH₃), 20.94 (OCOCH₃).

Analysis calculated for C₁₁H₁₁NO₂S requires:

C, 59.7; H, 5.0; N, 6.3; S, 14.5%.

Found: C, 59.6; H, 5.2; N, 6.2; S, 14.6%.

-124-

Reaction with phenyl isocyanate as above gave 2,2'-dithiobis[N-phenyl-5-acetoxy-1-methylindolyl-3-carboxamide] (91) [V: $R_1 = 5\text{-OAc}$, $R_2 = \text{CONHPh}$, $R_3 = \text{Me}$], (45% yield); mp 147-150°C.

5 $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{SO}$): δ 9.60 (1H, br, CONH), 7.54 (1H, d, $J = 1.9$ Hz, H-4), 7.42 (1H, d, $J = 8.9$ Hz, H-7), 7.23 (2H, d, $J = 7.8$ Hz, H-2',6'), 7.17 (2H, dd, $J = 7.8$, 7.1 Hz, H-3',5'), 7.06 (1H, dd, $J = 8.9$, 1.9 Hz, H-6), 6.98 (1H, t, $J = 7.1$ Hz, H-4), 3.66 (3H, s, NCH_3), 2.29 (3H, s, OCOCH_3).

10 $^{13}\text{H NMR}$: δ 169.52 (CONH), 161.18 (OCOCH_3), 145.27 (s), 138.49 (s), 135.41 (s), 128.31 (d), 125.46 (s), 122.94 (d), 119.15 (d), 112.82 (d), 111.43 (d), 30.26, (N- CH_3), 20.80 (OCOCH_3).

15 Analysis calculated for $\text{C}_{36}\text{H}_{30}\text{N}_4\text{O}_6\text{S}_2 \cdot 0.5\text{H}_2\text{O}$ requires:

C, 62.9; H, 4.5; N, 8.2; S, 9.3%.

Found: C, 63.1; H, 4.6; N, 8.2; S, 9.5%.

Compound 92 of Table 1

20 A stirred suspension of the 5-acetoxydisulfide (91) (0.25 g, 0.37 mmol) in MeOH (15 mL) was treated with NaBH_4 (0.05 g, 1.32 mmol) at 20°C for 10 minutes. Aqueous 3N KOH (2 mL) was then added, and after a further 15 minutes the solution was diluted with water and extracted with CH_2Cl_2 . The resulting oil was immediately dissolved in MeOH (3 mL) and mixed with H_2O_2 (0.10 mL of 35%). The solution was chilled at -30°C for 48 hours and then filtered to yield 2,2'-dithiobis(N-phenyl-5-hydroxy-1-methylindole-3-carboxamide) (92) [V: $R_1 = 5\text{-OH}$, $R_2 = \text{CONHPh}$, $R_3 = \text{Me}$] (41 mg, 19%); mp 185-187°C.

30 $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{SO}$): δ 9.50 (1H, s, CONH), 9.15 (1H, br, OH), 7.32 (2H, d, $J = 7.8$ Hz, H-2',6'), 7.27 (1H, d, $J = 8.9$ Hz, H-7), 7.19 (1H, d, $J = 2.3$ Hz, H-4), 7.18

-125-

(2H, dd, $J = 7.8, 7.4$ Hz, H-3',5'), 6.99 (1H, t, $J = 7.4$ Hz, H-4'), 6.83 (1H, dd, $J = 8.9, 2.3$ Hz, H-6), 3.51 (3H, s, N-CH₃).

Analysis calculated for C₃₂H₂₆N₄O₄S₂·H₂O requires:

5 C, 64.6; H, 4.4; N, 9.4%.

Found: C, 62.7; H, 4.6; N, 9.1%.

Compound 93 of Table 1

10 Similar demethylation/acetylation of 6-methoxy-1-methyl-2-oxindole [VII: R₁ = 6-OMe, R₃ = Me] gave 6-acetoxy-1-methyl-2-oxindole [VII: R₁ = 6-OAc, R₃ = Me] (81% yield); mp 119-121°C.

15 ¹H NMR (CDCl₃): δ 7.22 (1H, d, $J = 7.9$ Hz, H-4), 6.74 (1H, dd, $J = 7.9, 2.1$ Hz, H-5), 6.59 (1H, d, $J = 2.1$ Hz, H-7), 3.49 (2H, s, H-3), 3.18 (3H, s, N-CH₃), 2.31 (3H, s, OCOCH₃).

¹³C NMR: δ 175.28 (C-2), 169.57 (OCOCH₃), 150.74 (s), 146.23 (s), 124.83 (d), 121.81 (s), 115.00 (d), 102.68 (d), 35.33 (C-3), 26.27 (N-CH₃), 21.09 (OCOCH₃).

20 Analysis calculated for C₁₁H₁₁NO₃ requires:

C, 64.4; H, 5.4; N, 6.8%.

Found: C, 64.5; H, 5.5; N, 6.9%.

25 Reaction of this with P₂S₅ as above gave 6-acetoxy-1-methyl-2-indolinethione [IX: R₁ = 6-OAc, R₃ = Me] (91% yield); mp 131-133°C.

¹H NMR: δ (CDCl₃) 7.27 (1H, d, $J = 8.0$ Hz, H-4), 6.87 (1H, dd, $J = 8.0, 1.9$ Hz, H-5), 6.75 (1H, d, $J = 1.9$ Hz, H-7), 4.08 (2H, s, H-3), 3.58 (s, N-CH₃), 2.33 (3H, s, OCOCH₃).

30 ¹³C NMR: δ 202.18 (C-2), 169.44 (OCOCH₃), 150.80 (s), 147.57 (s), 126.38 (s), 124.32 (d), 117.05 (d), 104.06 (d), 48.62 (C-3), 31.33 (N-CH₃), 21.09 (OCOCH₃).

-126-

Analysis calculated for $C_{11}H_{11}NO_2S$ requires:

C, 59.7; H, 5.0; N, 6.3; S, 14.5%.

Found: C, 59.4; H, 5.2; N, 6.1; S, 14.3%.

Reaction with phenyl isocyanate as above gave
5 2,2'-dithiobis[N-phenyl-6-acetoxy-1-methylindolyl-
3-carboxamide] (93) [V: $R_1 = 6\text{-OAc}$, $R_2 = \text{CONHPh}$,
 $R_3 = \text{Me}$] (53%); mp 219-222°C.

^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 9.71 (1H, br s, CONH), 7.78 (1H,
d, $J = 8.7$ Hz, H-4), 7.27 (3H, m, H-2',6'), 7.18 (2H,
10 dd, $J = 8.2, 7.3$ Hz, H-3',5'), 6.99 (1H, t, $J = 7.3$ Hz,
H-4'), 6.95 (1H, dd, $J = 8.7, 1.8$ Hz, H-5), 3.60 (3H,
s, NCH_3), 2.32 (3H, s, OCOCH_3).

^{13}C NMR: δ 169.31 (CONHPh), 161.23 (OCOCH_3), 147.99
(s), 138.54 (s), 137.66 (s), 128.29 (d), 123.13 (s),
15 122.98 (d), 121.48 (d), 119.38 (d), 118.73 (s), 116.34
(d), 103.76 (d), 30.17 (N- CH_3), 20.81 (OCOCH_3).

Analysis calculated for $C_{36}H_{30}N_4O_6S_2$ requires:

C, 63.7; H, 4.5; N, 8.3; S, 9.4%.

Found: C, 63.7; H, 4.4; N, 8.2; S, 9.8%.

20

Compound 94 of Table 1

Similar treatment of the 6-acetoxydisulfide (93)
gave 2,2'-dithiobis(6-hydroxy-1-methyl-N-phenyl-
1H-indole-3-carboxamide) (94) [V: $R_1 = 6\text{-OH}$,
25 $R_2 = \text{CONHPh}$, $R_3 = \text{Me}$]; mp 185-187°C (dec).

^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 10.01, 9.43 (2H, 2s, OH and
CONH), 7.76 (1H, d, $J = 7.9$ Hz, H-4), 7.35 (2H, d,
 $J = 7.6$ Hz, H-2',6'), 7.31 (1H, d, $J = 2.2$ Hz, H-7),
7.10 (2H, dd, $J = 7.6, 7.4$ Hz, H-3',5'), 6.95 (1H, t,
30 $J = 7.4$ Hz, H-4'), 6.71 (1H, dd, $J = 7.9, 2.2$ Hz, H-5),
3.58 (3H, s, NCH_3).

Analysis calculated for $C_{32}H_{26}N_4O_4S_2$ requires:

595.1474.

Found: $[\text{M} + \text{H}]^+$ 595.1483 (FABMS).

-127-

Compound 95 of Table 1

Similar demethylation/acetylation of
7-methoxy-1-methyl-2-oxindole [VII: $R_1 = 7\text{-OMe}$,
 $R_3 = \text{Me}$] gave 7-acetoxy-1-methyl-2-oxindole

5 [VII: $R_1 = 7\text{-OAc}$, $R_3 = \text{Me}$] (68% yield); mp 95-97°C.
 $^1\text{H NMR}$ (CDCl_3): δ 7.12 (1H, dd, $J = 7.1, 1.0$ Hz, H-6),
7.01 (1H, dd, $J = 8.4, 7.1$ Hz, H-5), 6.96 (1H, dd,
 $J = 8.4, 1.0$ Hz, H-4), 3.54 (2H, s, H-3), 3.34 (3H, s,
N-CH₃), 2.35 (3H, s, OCOCH₃).

10 $^{13}\text{C NMR}$: δ 174.88 (C-2), 169.57 (OCOCH₃), 136.11 (s),
134.24 (s), 126.73 (s), 123.02 (d), 122.60 (d), 122.18
(d), 35.68 (C-3), 28.17 (N-CH₃), 20.89 (OCOCH₃).

Analysis is calculated for $\text{C}_{11}\text{H}_{11}\text{NO}_3$ requires:

C, 64.4; H, 5.4; N, 6.8%.

15 Found: C, 64.5; H, 5.5; N, 6.7%.

Reaction of this with P_2S_5 as above gave
7-acetoxy-1-methyl-2-indolinethione [IX: $R_1 = 7\text{-OAc}$,
 $R_3 = \text{Me}$] (85% yield); mp 133-135°C.

20 $^1\text{H NMR}$ (CDCl_3): δ 7.17 (1H, d, $J = 7.9$ Hz, H-6), 7.14
(1H, dd, $J = 8.0, 7.9$ Hz, H-5), 7.01 (1H, d,
 $J = 8.0$ Hz, H-4), 4.13 (2H, s, H-3), 3.78 (3H, s,
N-CH₃), 2.39 (3H, s, OCOCH₃).

25 $^{13}\text{C NMR}$: δ 202.00 (C-2), 169.22 (OCOCH₃), 137.53 (s),
134.33 (s), 131.42 (s), 124.78 (d), 123.23 (d), 121.69
(d), 49.20 (C-3), 33.67 (N-CH₃), 20.97 (OCOCH₃).

Analysis calculated for $\text{C}_{11}\text{H}_{11}\text{NO}_2\text{S}$ requires:

C, 59.7; H, 5.0; N, 6.3; S, 14.5%.

Found: C, 59.4; H, 5.2; N, 6.2; S, 14.2%.

Reaction with phenyl isocyanate as above gave
30 2,2'-dithiobis[*N*-phenyl-7-acetoxy-1-methylindolyl-
3-carboxamide] (95) [V: $R_1 = 7\text{-OAc}$, $R_2 = \text{CONHPh}$,
 $R_3 = \text{Me}$]; mp 212-214.5°C.

$^1\text{H NMR}$ ($(\text{CD}_3)_2\text{SO}$): δ 10.28 (1H, br, CONH), 7.72 (1H,
d, $J = 7.8$ Hz, H-4), 7.44 (2H, d, $J = 7.8$ Hz, H-2',6'),

-128-

7.23 (2H, dd, $J = 8.1, 7.8$ Hz, H-3',5'), 7.11 (1H, dd, $J = 7.8, 7.7$ Hz, H-5), 7.01 (2H, m, H-6, H-4'), 3.68 (3H, s, N-CH₃), 2.35 (3H, s, OCOCH₃).

¹³C NMR: δ 169.49 (CONHPh), 161.36 (OCOCH₃), 138.75 (s), 135.92 (s), 129.43 (s), 128.80 (s), 128.43 (d), 128.0 (s), 123.13 (d), 121.21 (d), 119.35 (d), 118.50 (d), 118.16 (d), 31.84 (OCOCH₃), 20.68 (N-CH₃).

Analysis calculated for C₃₆H₃₀N₄O₆S₂·0.5H₂O requires:

C, 62.9; H, 4.5; N, 8.2; S, 9.3%.

Found: C, 62.9; H, 4.5; N, 7.8; S, 9.6%.

Compound 96 of Table 1

Reaction of 96 as above with NaBH₄ followed by 3N KOH gave, after reoxidation, 2,2'-dithiobis(*N*-phenyl-7-hydroxy-1-methylindole-3-carboxamide) (96) [V:

R₁ = 7-OH, R₂ = CONHPh, R₃ = Me] (81% yield); mp 207°C (dec).

¹H NMR ((CD₃)₂SO): δ 9.94, 9.63 (each 1H, 2s, CONH and ArOH), 7.33 (1H, d, $J = 8.0$ Hz, H-2',6'), 7.23 (1H, d, $J = 8.0$ Hz, H-4), 7.18 (2H, dd, $J = 8.0, 8.0$ Hz, H-3',5'), 6.99 (1H, t, $J = 8.0$ Hz, H-4'), 6.91 (1H, dd, $J = 8.0, 7.5$ Hz, H-5), 6.65 (1H, d, $J = 7.5$ Hz, H-6), 3.89 (3H, s, N-CH₃).

¹³C NMR: δ 161.89 (CONH), 144.46 (s), 138.72 (s), 128.30 (d), 127.74 (s), 127.57 (s), 122.98 (d), 121.76 (d), 119.46 (d), 119.36 (s), 119.32 (s), 111.57 (d), 108.85 (d), 32.84 (N-CH₃).

Analysis calculated for C₃₂H₂₆N₄O₄S₂ requires:

C, 64.3; H, 4.4; N, 9.4; S, 10.8%.

Found: C, 64.2; H, 4.4; N, 9.3; S, 10.9%.

-129-

Compound 97 of Table 1

Similarly was prepared, from
1-methyl-2-indolinethione and methyl isocyanate,
bis[N-methyl 1-methylindolyl-3-carboxamide-(2)]-
5 disulfide [V: $R_1 = H$, $R_2 = CONHMe$, $R_3 = Me$] (97) (18%
yield); mp 162-165°C.

1H NMR ($CDCl_3$): δ 8.07 (1H, d, $J = 8.0$ Hz, H-4),
7.40-7.20 (3H, m, H-5, H-6, H-7), 6.31 (1H, br, CONH),
3.82 (3H, s, NCH_3), 2.13 (3H, d, $J = 5.0$ Hz, $CONHCH_3$).

10 ^{13}C NMR ($CDCl_3$): δ 173.29 (CONH), 128.34 (s), 125.28,
122.31, 122.02, 120.0 (s), 116.5 (s), 113.2 (s),
110.06, 30.26 ($N-CH_3$), 25.68 ($CONHCH_3$).

Alternate Preparation of Compound 97 of Table 1

15 A mixture of 20 g (136 mmol) of 1-methyl-
2-indolinone and 250 mL of dichloroethane was sealed in
a 500 mL stainless steel autoclave. The reactor was
cooled to less than -10°C and 60 g of phosgene was
distilled into the vessel. The reactor was sealed and
20 heated to 80°C while rocking. After 1 hour, the
reactor was cooled to room temperature, vented, and
purged with nitrogen. The reactor was opened and the
solution was rinsed out with fresh dichloromethane.
The dichloroethane solution from the rinsed reactor was
25 concentrated to a purple solid. The solid was
dissolved into 300 mL of dichloromethane and the
solution was cooled in an ice bath. Into the cold
solution was bubbled anhydrous methylamine at a
moderate rate over a 50-minute period. The mixture was
30 washed with water (2 x 300 mL) and brine, dried
(Na_2SO_4), and concentrated to ca. 150 mL. The solution
was purified by flash silica gel chromatography
(7.5 x 13 cm bed) eluting with 1.6 L dichloromethane,
2 L 2%, then 2 L 5% acetone/dichloromethane, with

-130-

500 mL fractions collected. Impure early product fractions were combined, concentrated, and recrystallized from 40 mL ethanol/12 mL pet ether to give 3.04 g of 2-chloro-1-methylindole-3-N-methylcarboxamide [XXII: $R_6 = H$, $R_7 = CH_3$]; mp 148-151°C. Pure product fractions were combined and concentrated to give 16.41 g of additional product as a pale yellow solid; mp 150-151°C. Total yield = 19.45 g (64%).

Reaction of 9.30 g (41.8 mmol) of the above carboxamide was carried out with 129.5 mmol of MeSLi in 36 mL of DMA. After heating at 60°C for 7 hours, the clear amber solution was cooled in an ice bath and treated slowly with 150 mL of 5% aqueous HCl. The resultant suspension was diluted with ca. 150 mL of dichloromethane, and the mixture was stirred for 1 hour. The layers were separated, and the aqueous phase was extracted twice more. The combined organic extracts were washed with water (3 x 200 mL), then brine, dried $MgSO_4$, and concentrated to a residue that was pumped at 0.05 mm for 1 hour to leave 12.5 g of an orange solid. The solid was suspended into 100 mL of HOAc and 50 mL of water, and with vigorous stirring the suspension was treated with 12.85 g of sodium perborate. The thick suspension was stirred for ca. 30 minutes, then filtered using 10% methanol in water to aid in the transfer. The solids were washed well with water, then with ether, and air dried. Further drying at 200 mm/65°C/overnight over P_2O_5 afforded 6.38 g (70%) of pure bis[N-methyl 1-methylindolyl-3-carboxamide-(2)]disulfide (97) [V: $R_2 = CONHCH_3$]; mp 186-187°C.

-131-

Compound 98 of Table 1

Similarly was prepared, from 1-methyl-2-indolinethione and benzyl isocyanate, bis[N-benzyl 1-methylindolyl-3-carboxamide-(2)]disulfide [V:

5 $R_1 = H$, $R_2 = CONHCH_2Ph$, $R_3 = Me$] (98) (0.12 g, 22%); mp 145-147°C.

1H NMR ($CDCl_3$): δ 8.13 (1H, d, $J = 8.1$ Hz, H-4), 7.38 (1H, t, $J = 7.4$ Hz, H-6), 7.31-7.20 (6H, m, H-5 and CH_2Ph), 7.11 (1H, d, $J = 7.4$ Hz, H-7), 6.60 (1H, br, CONH), 3.75 (2H, br, $COCH_2Ph$), 3.64 (3H, s, N- CH_3).
10 ^{13}C NMR ($CDCl_3$): δ 163.42 (\underline{CONH}), 138.37 (s), 128.59, 128.54 (s), 127.63 (s), 127.52, 127.40 (s), 127.20, 126.40 (s), 125.39, 122.52, 122.32, 110.30 (C-7), 42.94 (CH_2Ph), 30.24 (N- CH_3).

15 Analysis calculated for $C_{34}H_{30}N_4O_2S_2$ requires:

C, 69.1; H, 5.2; N, 9.5; S, 10.8%.

Found: C, 68.6; H, 5.3; N, 9.5; S, 10.6%.

EXAMPLE E

20 Preparation of Compounds 19 and 83 of Table 1 by the Method of Scheme 4

A mixture of 2-amino-3-methylpyridine (43.28 g, 0.4 mol) and benzotriazole (47.65 g, 0.4 mol) in EtOH (500 mL) was treated over 5 minutes with formaldehyde (32.2 g of 37% solution, 0.4 mol). The mixture was
25 stirred at 20°C overnight, then cooled and filtered to give 2-[(1-benzotriazolyl)methyl]-3-methyl pyridine (30 g, 31%). A sample was crystallized from EtOH; mp 175-177°C.

30 1H NMR ($CDCl_3$): δ 8.10 (1H, d, $J = 5$ Hz, H-8), 8.10 and 8.00 (2H, 2d, $J = 8$ Hz, H-4',7'), 7.45 and 7.33 (2H, 2t, $J = 8$ Hz, H-5',6'), 7.25 (1H, d, $J = 7$ Hz, H-4), 6.54 (1H, dd, $J = 7.5$ Hz, H-5), 6.47 (2H, d,

-132-

$J = 7$ Hz, CH_2), 5.38 (1H, t, $J = 7$ Hz, NH), 2.07 (3H, s, CH_3).

Crude 2-[(1-benzotriazolyl)methyl]-3-methylpyridine (30 g, 125 mmol) was suspended in dioxan (400 mL) and treated with NaBH_4 (5 g, 130 mmol). The mixture was heated under reflux for 8 hours, then the majority of the solvent was removed under reduced pressure. The residue was partitioned between toluene and water, and the organic layer was washed successively with dilute NaOH solution and water, and dried. Removal of the solvent gave 2-methylamino-3-methylpyridine as an oil (12.8 g, 84%).

^1H NMR (CDCl_3): δ 8.04 (1H, d, $J = 5.1$ Hz, H, H-6), 7.19 (1H, d, $J = 7.1$ Hz, H-4), 6.50 (1H, dd, $J = 7.1$, 5.1 Hz, 5-H), 4.15 (1H, m, NH), 3.03 (3H, d, $J = 4.5$ Hz, CH_3N), 2.06 (3H, s, CH_3).

^{13}C NMR (CDCl_3): δ 157.3 (C-2), 145.0 (C-8), 136.1 (C-4), 116.4 (C-3), 111.9 (C-5), 28.3 (CH_2) and 16.5 (CH_3).

A solution of the above pyridine (6.1 g, 50 mmol) in dry THF (150 mL) was cooled to -78°C under dry N_2 , and $n\text{-BuLi}$ (19.6 mL of a 2.5 M solution in hexanes, 50 mmol) was added dropwise, followed by $t\text{-BuLi}$ (32 mL of a 1.7 M in pentane, 55 mmol). The resulting mixture was allowed to warm to -20°C and maintained at that temperature for 30 minutes before being re-cooled to -78°C and treated with dry CO_2 gas until the mixture was decolorized. After warming to 20°C , the mixture was acidified with dilute HCl, and the solvent was removed under reduced pressure. The residue was dissolved in EtOH (100 mL) containing $p\text{-TsOH}$ (100 mg), heated under reflux for 3 hours to effect ring closure, and neutralized with aqueous ammonia. Solvent was then removed, and the residue was worked up in EtOAc to give

-133-

an oil, which was extracted with hot hexane, charcoaled, and filtered through celite. Concentration of the solution and cooled, gave 1-methyl-7-aza-

5 (2,3-bipyridin-2-one) [VII: $R_1 = 7\text{-aza}$, $R_3 = \text{Me}$] (1.2 g, 15%); mp (hexane) 94-96°C.

^1H NMR (CDCl_3): δ 8.15 (1H, d, $J = 5.3$ Hz, H-8), 7.48 (1H, d, $J = 7.2$ Hz, H-4), 8.94 (1H, dd, $J = 7.2$, 5.3 Hz, H-5), 3.53 (2H, s, CH_2), 3.29 (3H, s, CH_3).

10 ^{13}C NMR (CDCl_3): δ 174.1 (C-2), 158.1 (C-7a), 146.6 (C-8), 131.3 (C-4), 119.0 (C-3a), 117.8 (C-5), 34.6 (CH_2), 25.1 (CH_3).

P_2S_5 (3.80 g, 8.10 mmol) was added to a vigorously stirred suspension of Na_2CO_3 (0.88 g, 8.10 mmol) in THF

15 (30 mL). After the mixture had become homogeneous (ca. 15 minutes), a solution of 1-methyl-7-aza-2-indolinone [VII: $R_1 = 7\text{-aza}$, $R_3 = \text{Me}$] (1.00 g) in THF (10 mL) was added and stirring was continued for 18 hours at 20°C. Solvent was removed under reduced

20 pressure, and the residue was partitioned between EtOAc and water. Workup of the organic layer, and chromatography of the residue on silica gel (elution with EtOAc/petroleum ether (1:5)) gave 1-methyl-7-aza-

25 2-indolinethione [IX: $R_1 = 7\text{-aza}$, $R_3 = \text{Me}$] (0.81 g, 73%); mp (EtOAc/petroleum ether) 130-133°C.

^1H NMR (CDCl_3): δ 8.28 (1H, dd, $J = 5.2$, 0.6 Hz, H-6), 7.57 (1H, dd, $J = 7.3$, 0.6 Hz, H-4), 7.07 (1H, dd, $J = 7.3$, 5.2 Hz, H-5), 4.06 (2H, s, H-3), 3.66 (3H, s, N- CH_3).

30 ^{13}C NMR: δ 201.70 (C-2), 159.21 (s), 147.22 (d), 131.39 (d), 123.20 (s), 119.34 (d), 46.98 (C-3), 30.02 (N- CH_3).

-134-

Analysis calculated for $C_8H_8N_2S$ requires:

C, 58.5; H, 4.9; N, 17.1; S, 19.5%.

Found: C, 58.3; H, 4.9; N, 17.0; S, 19.8%.

A solution of the above thione (0.70 g, 4.26 mmol) in THF (5 mL) was added dropwise over 5 minutes under N_2 to an ice-cooled suspension of NaH (0.2 g of a 60% w/w dispersion in oil, 6.11 mmol). After gas evolution had ceased (5 minutes), phenyl isocyanate (0.47 mL, 4.25 mmol) was added, and stirring was continued for 1 hour at 20°C. Aqueous 1N HCl was then added, and the mixture was extracted with EtOAc. The organic layer was worked up, and the residue was chromatographed on silica gel. Elution with EtOAc/petroleum ether (1:1) and EtOAc gave foreruns, while elution with EtOAc/MeOH (10:1) gave N-phenyl (1-methyl-7-aza-2-thioxo-3-indoliny)carboxamide (19) [IV: R_1 = 7-aza, R_2 = CONHPh, R_3 = Me] as a fluorescent green solid (0.67 g, 55% yield); mp (after trituration with MeOH) 162-164°C (dec).

1H NMR ($(CD_3)_2SO$): δ 12.46 (1H, s, CONH), 8.68 (1H, dd, J = 7.7, 1.0 Hz, H-6), 8.02 (1H, d, J = 6.0 Hz, H-4), 7.72 (2H, d, J = 8.4 Hz, ArH), 7.36-7.29 (4H, m, ArH), 7.01 (1H, t, J = 7.3 Hz, ArH), 3.80 (3H, s, N-CH₃).

^{13}C NMR: δ 66.96 (C-2), 163.59 (CONH), 140.77 (s), 139.81 (s), 129.29 (d), 128.85 (d), 127.21 (s), 126.84 (d), 122.16 (d), 118.65 (d), 115.92 (d), 48.57 (C-3), 29.18 (N-CH₃).

Analysis calculated for $C_{15}H_{13}N_3O_2S \cdot CH_3OH$ requires:

C, 60.9; H, 5.4; N, 13.3; S, 10.2%.

Found: C, 60.6; H, 5.4; N, 13.4; S, 10.3%.

A solution of sodium perborate (0.50 g, 5.00 mmol) in water (25 mL) was added to a vigorously stirred suspension of the above 7-aza compound (19) (0.50 g,

-135-

176 mmol) in glacial AcOH (50 mL). After 1 hour the solid was filtered off, washed sequentially with water and Et₂O, and dried to give 2,2'-dithiobis[N-phenyl-1-methyl-7-azaindolyl-3-carboxamide] [V: R₁ = 7-aza, R₂ = CONHPh, R₃ = Me] (83) (100%); mp 197-198°C.

¹H NMR ((CD₃)₂SO): δ 9.49 (1H, s, CONH), 8.36 (1H, dd, J = 4.5, 1.5 Hz, H-6), 8.14 (1H, dd, J = 7.9, 1.5 Hz, H-4), 7.19 (1H, dd, J = 7.9, 4.5 Hz, H-5), 7.16-7.09 (4H, m, ArH), 6.98 (1H, m, ArH), 3.75 (3H, s, N-CH₃).

¹³C NMR: δ 160.42 (CONH), 147.58 (s), 145.99 (d), 138.29 (s), 129.86 (s), 129.62 (d), 128.25 (d), 123.05 (d), 119.23 (d), 118.09 (s), 117.76 (d), 117.57 (s), 28.61 (N-CH₃).

Analysis calculated for C₃₀H₂₄N₆O₂S₂·2.5H₂O requires:

C, 59.1; H, 4.8; N, 13.8; S, 10.5%.

Found: C, 59.1; H, 4.2; N, 13.8; S, 10.5%.

EXAMPLE F

Preparation of Compound 99 of Table 1 by the Method Outlined in Scheme 5

A solution of 2-[(4-methylphenylsulfonyl)methyl]-aniline [XII: R₁ = H, R₂ = Me, X = 4-methylphenyl] (Le Corre M, Hercouet A, Le Stanc Y, Le Baron H, Tetrahedron 1985;22:5313) in dry THF (60 mL), under N₂, was cooled to -78°C and n-butyllithium (9.6 mL, 2.5 M solution in hexanes) was added dropwise. The mixture was allowed to warm to -10°C to give a deep red colored solution which was recooled to -78°C after 30 minutes. CS₂ (3 mL, 5 mmol) was added rapidly, and the mixture was allowed to warm slowly to 20°C. The solvent was removed under vacuum and the residue was diluted with water, and acidified with 2 M HCl. After stirring at 20°C for 3 hours, the solution was extracted with EtOAc and dried (Na₂SO₄). The solvent was removed, and

-136-

chromatography of the residue on SiO₂ (CH₂Cl/EtOAc, 9:1) gave bis[3-(4-methylphenylsulfonyl)-2-indolyl]-disulfide [XIII: R₁ = H, R₂ = Me, X = 4-methylphenyl] (99) (0.2 g, 7% yield); mp (benzene) 230-233°C.

5 ¹H NMR (CDCl₃): δ 8.06 (1H, m, NH), 7.91 (3H, m, H-4, H-2, and H-4'), 7.45 (1H, m, H-6), 7.21 (4H, m, H-5, H-7, H-3', and H-5'), 2.33 (3H, s, CH₃).

10 ¹³C NMR (CDCl₃): δ 144.1, 140.0, 136.6, 134.0, 129.9 (CH), 126.4 (CH), 125.4, 124.5 (CH), 122.8 (CH), 119.1 (CH), 115.1, 112.2 (CH), and 21.5 (CH₃).

Analysis calculated for C₃₀H₂₄N₂O₄S₄·0.2(C₆H₆) requires:

C, 60.4; H, 4.1; N, 5.5; S, 20.7%.

Found: C, 60.7; H, 4.4; N, 4.9; S, 21.1%.

15

EXAMPLE G

Preparation of Compounds 24 and 100 of Table 1 by the Method Outlined in Scheme 6

20 A stirred solution of benzoyl chloride (from benzoic acid, 0.45 g, 3.68 mmol) in Me₂CO (20 mL) was treated dropwise at 0°C with a solution of NaN₃ (0.26 g, 3.98 mmol) in water (2 mL). After 15 minutes the solution was partitioned between water and benzene, and the organic layer was washed well with NaHCO₃ and worked up to give crude phenacyl azide, which was used
25 directly.

30 A solution of 1-methyl-2-indolinethione (0.50 g, 3.06 mmol) in dry THF (3 mL) was added dropwise at 20°C under N₂ to a stirred suspension of NaH (0.13 g of a 60% w/w suspension in mineral oil, 3.37 mmol) in THF (2 mL). After gas evolution had ceased (5 minutes), a solution of the above phenacyl azide in THF (2 mL) was added dropwise, and the mixture was stirred at 20°C for 1 hour, then poured into 6N HCl and extracted with EtOAc. The residue from the organic layer was

-137-

chromatographed on silica gel. Elution with CH_2Cl_2 /petroleum ether (3:7) gave foreruns, and elution with CH_2Cl_2 /petroleum ether (2:3) gave 3-benzoyl-1-methyl-2-indolinethione [XV: $R_1 = \text{H}$, $R_3 = \text{Me}$, $R_5 = \text{C}_6\text{H}_5$] (24) (0.31 g, 38%); mp (trituration from MeOH) 132-134°C.

^1H NMR (CDCl_3): δ 15.83 (1H, s, SH), 7.68-7.53 (5H, m, C₆Ph), 7.21 (1H, dd, $J = 8.1, 7.3$ Hz, H-5), 7.11 (1H, d, $J = 8.1$ Hz, H-4), 6.90 (1H, dd, $J = 8.0, 7.3$ Hz, H-6), 6.76 (1H, d, $J = 8.0$ Hz, H-7), 3.74 (3H, s, NCH_3).

^{13}C NMR (CDCl_3): δ 181.71 (C₆Ph), 175.09 (C-2), 141.42 (s), 134.87 (s), 131.29, 128.85, 128.37, 125.64 (4xd), 125.22 (s), 122.81, 120.31 (2xd), 111.77 (s), 109.129 (d), 29.57 (NCH_3).

Analysis calculated for $\text{C}_{16}\text{H}_{13}\text{NOS}$ requires:

C, 71.9; H, 4.9; N, 5.2; S, 12.0%.

Found: C; 71.6; H, 5.1; N, 6.2; S, 13.9%.

A solution of 24 (0.10 g, 0.37 mmol) in CH_2Cl_2 (20 mL) was treated dropwise at 20°C with a solution of I_2 (0.50 g) in CH_2Cl_2 (5 mL), until TLC indicated complete conversion (ca. 2 hours). The solution was concentrated to ca. 1 mL and chromatographed directly on silica gel. Elution with CH_2Cl_2 gave traces of I_2 and starting material, and further elution with

CH_2Cl_2 /MeOH (19:1) gave bis[3-benzoyl-1-methylindole-(2)]disulfide [XVI: $R_1 = \text{H}$, $R_3 = \text{Me}$, $R_5 = \text{C}_6\text{H}_5$] (100) (0.06 g, 61%); mp (CHCl_3 /petroleum ether) 199-202°C.

^1H NMR (CD_3SOCD_3): δ 7.56 (1H, d, $J = 8.4$ Hz, H-4), 7.50 (1H, d, $J = 8.1$ Hz, H-7), 7.46 (dd, $J = 8.1, 7.4$ Hz, H-6), 7.35 (1H, dd, $J = 8.4, 7.4$ Hz, H-5), 7.19 (3H, m, H-2', 4', 6'), 6.92 (2H, d, $J = 7.1$ Hz, H-3', 5'), 3.48 (3H, s, NCH_3).

^{13}C NMR (CD_3SOCD_3): δ 190.20 (C₆Ph), 140.05, 138.03, 132.75 (3xs), 131.60, 128.48, 127.88 (3xd), 126.00 (s),

-138-

124.78, 122.27 (2xd), 122.03 (s), 121.03, 111.20 (2xd),
30.37 (NCH₃).

Analysis calculated for C₃₂H₂₄N₂O₂S₂ requires:

C, 69.8; H, 4.8; N, 5.1; S, 11.6%.

5 Found: C, 70.3; H, 4.7; N, 5.2; S, 11.3%.

Compounds 25, 26, 101, and 102 of Table 1

Similar treatment of 1-methyl-2-indolinethione
with 4-carbomethoxybenzoyl azide gave 3-(4'-carbo-
10 methoxybenzoyl)-1-methyl-2-indolinethione [XV: R₁ = H,
R₃ = Me, R₅ = 4-MeOOCCH₂CH₃] (26) (68%); mp 164-166°C.

¹H NMR (CDCl₃): δ 15.85 (1H, s, SH), 8.23 (2H, d,
J = 8.3 Hz, H-3',5'), 7.76 (2H, d, J = 8.3 Hz,
H-2',6'), 7.23 (1H, dd, J = 8.0, 7.6 Hz, H-5'), 7.12
15 (1H, d, J = 7.6 Hz, H-4), 6.90 (1H, dd, J = 8.0,
7.9 Hz, H-6), 6.69 (1H, d, J = 7.9 Hz, H-7), 3.99 (3H,
s, COOCH₃), 3.74 (3H, s, NCH₃).

¹³C NMR (CDCl₃): δ 182.07 (COAr), 173.27 (C-2), 166.31
(COOCH₃), 141.59, 138.92, 132.51 (3xs), 130.11, 128.54,
20 126.04 (3xd), 124.76 (s), 123.00, 120.26 (2xd), 119.95
(s), 109.28 (d), 52.50 (COOCH₃), 29.61 (NCH₃).

Analysis calculated for C₁₈H₁₅NO₃S requires:

C, 66.4; H, 4.7; N, 4.3; S, 9.8%.

Found: C, 66.5; H, 4.7; N, 4.6; S, 9.8%.

25 Oxidation of 26 with I₂/CH₂Cl₂ as above gave
bis[3-(4'-carbomethoxybenzoyl)-1-methylindole-(2)]-
disulfide [XVI: R₁ = H, R₃ = Me, R₅ = 4-MeOOCCH₂CH₃]
(102); mp (CHCl₃/petroleum ether) 200-203°C.

¹H NMR (CD₃SOCD₃): δ 7.74 (2H, d, J = 8.4 Hz,
30 H-3',5'), 7.67 (1H, d, J = 8.0 Hz, H-4), 7.64 (1H, d,
J = 8.4 Hz, H-7), 7.44 (1H, dd, J = 8.4, 8.0 Hz, H-6),
7.27 (1H, dd, J = 8.0, 8.0 Hz, H-5), 6.99 (2H, d,
J = 8.4 Hz, H-2',6'), 3.91 (3H, s, COOCH₃), 3.51 (3H,
s, NCH₃).

-139-

^{13}C NMR (CD_3SOCD_3): δ 189.31 (COAr), 165.56 (COOCH_3), 143.77, 137.98, 133.31, 131.61 (4xs), 128.50, 128.33 (2xd), 125.87 (s), 124.99, 122.62 (2xd), 121.27 (s), 121.09, 111.22 (2xd), 52.34 (COOCH_3), 30.33 (NCH_3).

5 Analysis calculated for $\text{C}_{36}\text{H}_{28}\text{N}_2\text{O}_6\text{S}_2$ requires:

C, 66.6; H, 4.4; N, 4.3; S, 9.9%.

Found: C, 66.2; H, 4.8; N, 4.4; S, 9.9%.

A suspension of 26 (0.1 g, 0.31 mmol) in MeOH (5 mL) containing 3N NaOH (2 mL) was stirred at 20°C for 3 hours, then concentrated to dryness. The residue was dissolved in water and acidified (concentrated HCl) to give 3-(4'-carboxybenzoyl)-1-methyl-2-indolinethione [XV: $\text{R}_1 = \text{H}$, $\text{R}_3 = \text{Me}$, $\text{R}_5 = 4\text{-HOOC}_6\text{H}_4$] (25) (100%); mp 282°C (dec).

15 ^1H NMR ($\text{CD}_3\text{SOCD}_3/\text{CD}_3\text{COCD}_3$): δ 15.90 (0.3H, br, SH), 13.00 (1H, br s, COOH), 8.26 (2H, d, $J = 8.2$ Hz, H-3',5'), 8.10 (0.6H, s, SH), 7.85 (2H, d, $J = 8.2$ Hz, H-2',6'), 7.40 (1H, d, $J = 8.0$ Hz, H-4), 7.29 (1H, dd, $J = 8.0, 8.0$ Hz, H-5), 6.98 (1H, dd, $J = 8.0, 7.5$ Hz, H-6), 6.68 (1H, d, $J = 7.5$ Hz, H-7), 3.77 (3H, s, NCH_3).

20 ^{13}C NMR $\text{CD}_3\text{SOCD}_3/\text{CD}_3\text{COCD}_3$: δ 167.57, 167.50 (COAr and COOH), 142.40, 135.64, 134.55 (3xs), 130.86, 130.18, 129.13, 126.93 (4xd), 125.17 (s), 123.81, 120.68 (2xd), 112.39 (s), 110.82 (d), 29.94 (NCH_3).

25 Analysis calculated for $\text{C}_{17}\text{H}_{13}\text{NSO}_3 \cdot \text{H}_2\text{O}$ requires:

C, 64.6; H, 4.3; N, 4.4; S, 10.1%.

Found: C, 64.6; H, 4.4; N, 4.0; S, 9.6%.

Similar hydrolysis of 102 gave bis[3-(4'-carboxybenzoyl)-1-methylindole-(2)]disulfide [XVI: $\text{R}_1 = \text{H}$, $\text{R}_3 = \text{Me}$, $\text{R}_5 = 4\text{-HOOC}_6\text{H}_4$] (101); mp (CHCl_3 /petroleum ether) 241-246°C.

30 ^1H NMR (CD_3SOCD_3): δ 12.62 (1H, br, COOH), 7.89 (3H, m, H-4 and H-3',5'), 7.74 (1H, d, $J = 8.5$ Hz, H-7),

-140-

7.58 (3H, m, H-6 and H-2',6'), 7.36 (1H, m, H-5), 3.66 (3H, s, NCH₃).

Analysis calculated for C₃₄H₂₄N₂O₆S₂·0.5·H₂O requires:

C, 63.1; H, 4.2%.

5 Found: C, 63.1; H, 5.3%.

EXAMPLE H

Preparation of Compounds 104 and 105 of Table 1 by the Method Outlined in Scheme 7

10 A solution of monomethyl terephthalate
[XVII: 4-COOMe] (1.32 g, 7.33 mmol) and DMF (1 drop)
in SOCl₂ (30 mL) was heated under reflux for
45 minutes, before concentration to dryness under
reduced pressure. The residue was dissolved in benzene
15 and evaporated to dryness again. The crude acid
chloride was dissolved in dry Me₂CO (20 mL), cooled to
0°C, and treated with a solution of NaN₃ (0.52 g,
8.00 mmol) in water (3 mL). After 20 minutes the
solution was diluted with water, extracted with CH₂Cl₂,
20 and worked up to give the crude acyl azide
[XVIII: 4-COOMe], which was immediately dissolved in
dry toluene (25 mL) and heated under reflux under N₂
for 2 hours. Concentration to dryness under reduced
pressure afforded the isocyanate [XIX: 4-COOMe] which
25 was used directly.

A solution of 1-methyl-2-indolinethione
[IV: R₁,R₂ = H, R₃ = CH₃] (1.00 g, 6.13 mmol) in THF
(2 mL) was added under N₂ to a suspension of NaH
(0.26 g of 60% w/w dispersion in mineral oil,
30 6.50 mmol) in THF (15 mL). After gas evolution had
ceased (5 minutes), a solution of the above crude
isocyanate in THF (10 mL) was added, and the solution
was stirred at 20°C for a further 1 hour. The mixture
was acidified with 3N HCl, extracted with EtOAc and

-141-

worked up to give an oily solid. Chromatography on silica gel, eluting with EtOAc, afforded a greenish solid. This was dissolved in MeOH and treated with 30% H₂O₂ (0.20 mL), and the resulting yellow precipitate was filtered off and washed well with MeOH to give 2,2'-dithiobis[N-(4'-carbomethoxy)phenyl-1-methylindolyl-3-carboxamide] (104) [XX: R = 4-COOMe] (0.74 g, 35%); mp 184-186°C.

¹H NMR ((CD₃)₂SO): δ 9.87 (1H, br, CONH), 7.80 (1H, d, J = 8.0 Hz, H-4), 7.74 (2H, d, J = 8.7 Hz, H-2',6'), 7.37 (1H, d, J = 8.3 Hz, H-7), 7.32 (2H, d, J = 8.7 Hz, H-3',5'), 7.26 (1H, dd, J = 8.3, 7.6 Hz, H-6), 7.15 (1H, dd, J = 8.0, 7.6 Hz, H-5), 3.84 (3H, s, CO₂CH₃), 3.66 (3H, s, N-CH₃).

¹³C NMR: δ 165.79 (COOCH₃), 161.56 (CONH), 143.01 (s), 137.68 (s), 129.79 (d), 125.41 (s), 124.35 (d), 123.37 (s), 121.40 (d), 120.82 (d), 119.90 (s), 118.33 (d), 117.93 (s), 110.74 (d), 51.74 (COOCH₃), 30.04 (N-CH₃).

Analysis calculated for C₃₆H₃₀N₄O₆S₂·H₂O requires:

C, 62.1; H, 4.6; N, 8.1; S, 9.2%.

Found: C, 62.2; H, 4.6; N, 8.0; S, 9.2%.

A suspension of (104) (0.23 g, 0.34 mmol) in MeOH (40 mL) was treated with 3N KOH (15 mL) and stirred at 20°C for 90 minutes. The resulting solution was filtered, acidified, and the resulting precipitate collected and re-dissolved in CH₂Cl₂ (10 mL) containing MeOH (1 mL). H₂O₂ (0.20 mL of 30%) was added, and after 1 hour the solvents were removed under reduced pressure. The residue was triturated with MeOH to give 2,2'-dithiobis[N-(4'-carboxy)phenyl-1-methylindolyl-3-carboxamide] (105) [XX: R = 4-COOH] (100% yield); mp 221°C (dec).

¹H NMR ((CD₃)₂SO): δ 12.63 (1H; br, COOH), 9.78 (1H, s, CONH), 7.80 (1H, d, J = 8.0 Hz, H-4), 7.72 (2H, d,

-142-

$J = 8.7$ Hz, H-3',5'), 7.39 (1H, d, $J = 8.4$ Hz, H-7), 7.30 (2H, d, $J = 8.7$ Hz, H-2',6'), 7.28 (t, $J = 8.4$, 7.7 Hz, H-6), 7.16 (1H, t, $J = 8.0$, 7.7 Hz, H-5), 3.66 (3H, s, N-CH₃).

5 ¹³C NMR: δ 166.95 (COOH), 161.58 (CONH), 142.67 (s), 137.78 (s), 129.99 (d), 129.81 (s), 125.41 (s), 124.72 (s), 124.54 (d), 121.50 (d), 120.93 (d), 118.39 (d), 110.89 (d), 30.12 (N-CH₃).

Analysis calculated for C₃₄H₂₆N₄O₆S₂·0.5H₂O requires:

10 C, 61.9; H, 4.1; N, 8.5; S, 9.7%.

Found: C, 61.6; H, 4.2; N, 8.4; S, 9.9%.

Compounds 106 and 107 of Table 1

Similar treatment of 1-methyl-2-indolinethione

15 [IV: R₁,R₂ = H, R₃ = CH₃] with the isocyanate [XIX: 3-COOMe] derived from monomethyl isophthalate gave 2,2'-dithiobis[N-(3'-carbomethoxy)phenyl-1-methylindolyl-3-carboxamide] (106) [XX: R = 3-COOMe] (57% yield); mp 193-195°C.

20 ¹H NMR ((CD₃)₂SO): δ 9.67 (1H, s, CONH), 7.96 (1H, br s, H-2'), 7.79 (1H, d, $J = 8.0$ Hz, H-4), 7.56 (1H, d, $J = 7.7$ Hz, H-6'), 7.45 (1H, d, $J = 8.2$ Hz, H-7), 7.34 (1H, d, $J = 8.3$ Hz, H-4'), 7.28 (1H, dd, $J = 8.3$, 7.7 Hz, H-5'), 7.21 (1H, dd, $J = 8.2$, 7.7 Hz, H-6), 25 7.10 (1H, dd, $J = 8.0$, 7.7 Hz, H-5), 3.88 (3H, s, COOCH₃), 3.66 (3H, s, N-CH₃).

¹³C NMR: δ 166.04 (COOCH₃), 161.48 (CONH), 138.89 (s), 137.63 (s), 129.77 (s), 129.54 (s), 128.62 (d), 125.21 (s), 124.39 (d), 123.51 (s), 121.28 (d), 120.83 (d), 30 119.50 (d), 118.31 (s), 110.64 (d), 51.99 (COOCH₃), 30.02 (N-CH₃).

Analysis calculated for C₃₆H₃₀N₄O₆S₂ requires:

C, 63.7; H, 4.5; N, 8.3; S, 9.5%.

Found: C, 63.9; H, 4.6; N, 8.4; S, 9.6%.

-143-

Hydrolysis of the ester (106) as above, followed by re-oxidation with $\text{H}_2\text{O}_2/\text{MeOH}$, gave 2,2'-dithiobis[N-(3-carboxy)phenyl-1-methylindolyl-3-carboxamide] (107) [XX: R = 3-COOH] (97% yield); mp 219-220°C.

- 5 ^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 12.68 (1H, br, COOH), 9.69 (1H, s, CONH), 7.98 (1H, br s, H-2'), 7.80 (1H, d, J = 8.0 Hz, H-4), 7.56 (1H, d, J = 7.7 Hz, H-6'), 7.43 (1H, d, J = 8.2 Hz, H-7), 7.36 (1H, d, J = 8.3, 7.7 Hz, H-4'), 7.24 (2H, m, H-5',6), 7.11 (1H, t, J = 8.0, 7.7 Hz, H-5), 3.66 (3H, s, N-CH₃).
- 10 ^{13}C NMR: δ 167.10 (COOH), 161.53 (CONH), 138.77 (s), 137.62 (s), 130.92 (s), 129.47 (s), 128.44 (d), 125.18 (s), 124.45 (d), 123.75 (d), 123.31 (d), 121.32 (d), 120.81 (d), 119.91 (d), 118.51 (s), 110.67 (d), 30.01 (N-CH₃).
- 15

Analysis calculated for $\text{C}_{34}\text{H}_{26}\text{N}_4\text{O}_6\text{S}_2 \cdot 0.5\text{H}_2\text{O}$ requires:

C, 61.9; H, 4.1; N, 8.5; S, 9.7%.

Found: C, 61.7; H, 4.3; N, 8.8; S, 9.7%.

20 Compounds 108 & 109 of Table 1

- Similar treatment of 1-methyl-2-indolinethione [IV: $\text{R}_1, \text{R}_2 = \text{H}$, $\text{R}_3 = \text{CH}_3$] with the isocyanate [XIX: 2-COOMe] derived from monomethyl phthalate gave 2,2'-dithiobis[N-(2-carbomethoxy)phenyl-1-methyl-indolyl-3-carboxamide] (108) [XX: R = 2-COOMe] (61% yield); mp 179-181°C.
- 25

- ^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 10.82 (1H, s, CONH), 7.89 (2H, 2xd, J = 8.3, 8.0 Hz, H-3',6'), 7.74 (1H, d, J = 8.3 Hz, H-4), 7.32 (2H, m, H-7,4'), 7.20 (1H, dd, J = 8.1, 7.5 Hz, H-6), 7.12 (1H, dd, J = 8.3, 7.5 Hz, H-5), 6.97 (1H, m, H-5'), 3.84 (3H, s, COOCH₃), 3.68 (3H, s, N-CH₃).
- 30

-144-

Analysis calculated for $C_{36}H_{30}N_4O_6S_2 \cdot 0.5H_2O$ requires:

C, 62.9; H, 4.5; N, 8.2; S, 9.3%.

Found: C, 62.8; H, 4.5; N, 8.1; S, 9.3%.

Hydrolysis of the ester (108) as above, followed
5 by re-oxidation with $H_2O_2/MeOH$, gave 2,2'-dithiobis[N-(2'-carboxy)phenyl-1-methylindolyl-3-carboxamide] (109)
[XX: R = 2-COOH] (91% yield); mp 184-186°C.

1H NMR ($(CD_3)_2SO$): δ 13.33 (1H, br, COOH), 11.31 (1H, s, CONH), 7.95 (1H, d, J = 8.1 Hz, H-6'), 7.90 (1H, d, J = 7.9 Hz, H-3'), 7.83 (1H, d, J = 8.3 Hz, H-4), 7.30
10 (2H, m, H-7,4'), 7.19 (1H, dd, J = 8.0, 7.5 Hz, H-6), 7.08 (1H, dd, J = 8.3, 7.5 Hz, H-5), 7.02 (1H, dd, J = 8.1, 7.8 Hz, H-5'), 3.67 (3H, s, N-CH₃).

^{13}C NMR: δ 169.16 (COOH), 160.71 (CONH), 140.55 (s),
15 137.78 (s), 133.31 (d), 130.50 (d), 129.30 (s), 125.01 (s), 124.50 (d), 121.79 (d), 121.47 (d), 121.05 (d), 120.28 (d), 118.21 (s), 115.91 (s), 110.68 (d), 29.93 (N-CH₃).

Analysis calculated for $C_{34}H_{26}N_4O_6S_2 \cdot 2H_2O$ requires:

20 C, 59.5; H, 4.4; N, 8.2; S, 9.3%.

Found: C, 59.3; H, 4.3; N, 8.3; S, 9.6%.

Compound 110 of Table 1

Similar treatment of 1-methyl-2-indolinethione
25 [IV: R_1, R_2 = H, R_3 = CH₃] with the isocyanate derived from 4-(carbomethoxy)phenylacetic acid gave
2,2'-dithiobis[N-(4'-carbomethoxy)benzyl
1-methylindolyl-3-carboxamide] (110) [V: R_1 = H,
 R_2 = CONHCH₂Ph{4-COOMe}, R_3 = Me] (38% yield);
30 mp 178-180°C.

1H NMR ($(CD_3)_2SO$): δ 8.18 (1H, br, CONH), 7.88 (1H, d, J = 8.1 Hz, H-4), 7.82 (2H, d, J = 7.9 Hz, C-2',6'),
7.55 (1H, d, J = 8.3 Hz, H-7), 7.35 (1H, dd, J = 8.3, 7.7 Hz, H-6), 7.28 (2H, d, J = 7.9 Hz, C-3',5'), 7.20

-145-

(1H, dd, $J = 8.1, 7.7$ Hz, H-5), 4.06 (2H, d, $J = 5.1$ Hz, CONHCH₂), 3.83 (3H, s, COOCH₃), 3.61 (3H, s, N-CH₃).

¹³C NMR: δ 165.98 (COOCH₃), 163.17 (CONH), 145.10 (s), 137.61 (s), 129.06 (d), 129.00 (s), 127.85 (s), 126.95 (d), 125.37 (s), 124.31 (d), 121.22 (d), 121.09 (d), 117.89 (s), 110.78 (d), 51.89 (COOCH₃), 41.90 (CH₂Ar), 29.94 (N-CH₃).

Analysis calculated for C₃₈H₃₄N₄O₆S₂·0.5H₂O requires:

C, 63.8; H, 4.9; N, 7.8; S, 8.9%.

Found: C, 63.7; H, 4.8; N, 7.8; S, 9.1%.

EXAMPLE I

Preparation of Compound 111 of Table 1 by the Method Outlined in Scheme 8.

A solution of 2-chloro-1-methylindole-3-carboxylic acid [XXI] (Marchetti L, Andreani A, Ann. Chim. (Rome) 1973;63:681) (0.95 g, 4.52 mmol) and SOCl₂ (0.99 mL, 13 mmol) in 1,2-dichloroethane (100 mL) containing DMF (1 drop) was heated under reflux under N₂ for 2 hours, then concentrated to dryness. The residue was dissolved in CH₂Cl₂ (50 mL) and treated with a slurry of methyl 4-(aminomethyl)benzoate hydrochloride (Nair MG, Baugh CM, J. Org. Chem. 1973;38:2185) (1.00 g, 4.98 mmol) and Et₃N (1.58 mL, 11 mmol) in CH₂Cl₂ (50 mL). After vigorous stirring at 20°C for 24 hours, the mixture was washed with water and the organic portion worked up to give N-(4'-carbomethoxy)-benzyl 2-chloro-1-methylindole-3-carboxamide [XXII: R₆ = H, R₇ = CH₂Ph{4-COOMe}] (1.40 g, 86%) which crystallized from aqueous acetone; mp 108-110°C. ¹H NMR ((CD₃)₂SO): δ 8.38 (1H, t, $J = 5.8$ Hz, CONHCH₂), 7.95 (2H, d, $J = 7.9$ Hz, H-2',6'), 7.91 (1H, d, $J = 7.8$ Hz, H-4), 7.56 (1H, d, $J = 7.9$ Hz, H-7), 7.52

-146-

(2H, d, $J = 7.9$ Hz, H-3',5'), 7.29 (1H, dd, $J = 7.9$, 7.1 Hz, H-6), 7.19 (1H, dd, $J = 7.8$, 7.1 Hz, H-5), 4.60 (2H, d, $J = 5.8$ Hz, CONHCH_2), 3.84 (3H, s, COOCH_3), 3.79 (3H, s, N- CH_3).

5 ^{13}C NMR: δ 166.09 (COOCH_3), 162.77 (CONH), 145.65 (s), 135.00 (s), 129.18 (d), 129.14 (d), 127.94 (s), 127.34 (d), 127.25 (d), 126.34 (s), 124.77 (s), 122.57 (d), 121.19 (d), 119.97 (d), 110.21 (s), 107.11 (d), 51.95 (COOCH_3), 42.15 (CH_2), 29.97 (N- CH_3).

10 Analysis calculated for $\text{C}_{19}\text{H}_{17}\text{ClN}_2\text{O}_3$ requires:

C, 64.0; H, 4.8; N, 7.9; Cl, 9.9%.

Found: C, 64.0; H, 4.8; N, 7.6; Cl, 9.8%.

A solution of the above carboxamide (1.00 g, 2.80 mmol) in DMA (10 mL) was added under N_2 to a stirred suspension of MeSLi (1.06 g, 19 mmol) in DMA
15 (25 mL). After warming at 80°C for 6 hours, the mixture was acidified with 3N HCl, extracted with CH_2Cl_2 , and worked up to give a yellow oil. Traces of DMA were removed under high vacuum, and the residue was
20 dissolved in MeOH (20 mL) and treated dropwise with H_2O_2 (0.60 mL of 30% solution). After chilling at -30°C overnight, the precipitate was filtered off, washed well with MeOH, and dried to give
25 2,2'-dithiobis[N-(4'-carboxy)benzyl 1-methylindol-3-carboxamide] (111) [V: $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CONHCH}_2\text{Ph}\{4\text{-COOH}\}$, $\text{R}_3 = \text{Me}$] (0.68 g, 72%); mp $178\text{-}180^\circ\text{C}$.

^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 12.86 (1H, br, COOH), 8.13 (1H, t, $J = 5.8$ Hz, CONHCH_2), 7.92-7.80 (3H, m, H-4,2',6'),
30 7.56 (1H, d, $J = 8.3$ Hz, H-7), 7.37 (1H, t, $J = 8.3$, 7.8 Hz, H-6), 7.27 (2H, d, $J = 6.3$ Hz, H-3',5'), 7.20 (1H, dd, $J = 8.1$, 7.8 Hz, H-5), 4.02 (2H, d, $J = 5.8$ Hz, CONHCH_2), 3.62 (3H, s, N- CH_3).

-147-

^{13}C NMR: δ 167.08 (COOH), 163.08 (CONH), 144.51 (s), 137.64 (s), 130.35 (s), 129.25 (d), 129.04 (s), 126.85 (d), 125.25 (s), 124.44 (d), 121.23 (d), 121.10 (d), 118.33 (s), 110.87 (d), 41.92 (CH_2), 29.94 (N- CH_3).

5 Analysis calculated for $\text{C}_{36}\text{H}_{30}\text{N}_4\text{O}_6\text{S}_2 \cdot 1.5\text{H}_2\text{O}$ requires:

C, 61.3; H, 4.7; N, 7.9; S, 9.1%.

Found: C, 61.1; H, 4.8; N, 8.3; S, 9.0%.

Compound 112 of Table 1

10 Similar reaction of 2-chloro-1-methylindole-3-carboxylic acid [XXI] with SOCl_2 and glycine methyl ester hydrochloride gave *N*-carbomethoxymethyl 2-chloro-1-methylindole-3-carboxamide [XXII: $\text{R}_6 = \text{H}$, $\text{R}_7 = \text{CH}_2\text{COOMe}$] (78% yield); mp (CHCl_3 /light petroleum) 102.5-104°C.

15 ^1H NMR (CDCl_3): δ 8.26 (1H, d, $J = 8.1$ Hz, H-4), 7.30-7.23 (3H, m, H-5,6,7), 6.96 (1H, br, CONH), 4.32 (2H, d, $J = 5.0$ Hz, CH_2NHCO), 3.81 (3H, s, COOCH_3), 3.75 (3H, s, N- CH_3).

20 ^{13}C NMR: δ 170.91 (COOCH_3), 163.48 (CONH), 135.45 (s), 126.90 (s), 125.93 (s), 123.24 (d), 122.25 (d), 121.30 (d), 109.26 (d), 106.32 (s), 52.41 (COOCH_3), 41.38 (CH_2COOMe), 30.11 (N- CH_3).

Analysis calculated for $\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{O}_3$ requires:

25 C, 55.6; H, 4.7; N, 10.0%.

Found: C, 55.3; H, 4.8; N, 10.2%.

Treatment of this with MeSLi as above gave 2,2'-dithiobis[*N*-carboxymethyl 1-methylindolyl-3-carboxamide] (112) [V: $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CONHCH}_2\text{COOH}$, $\text{R}_3 = \text{Me}$] (56% yield); mp 197°C (dec).

30 ^1H NMR ((CD_3) $_2\text{SO}$): δ 7.98 (1H, d, $J = 8.1$ Hz, H-4), 7.59 (1H, br, CONH), 7.55 (1H, d, $J = 8.4$ Hz, H-7), 7.35 (1H, dd, $J = 8.4, 7.5$ Hz, H-6), 7.20 (1H, dd,

-148-

$J = 8.1, 7.5$ Hz, H-5), 3.68 (3H, s, N-CH₃), 3.20 (2H, d, $J = 5.2$ Hz, CH₂COOH).

¹³C NMR: δ 171.02 (COOH), 162.57 (CONH), 137.60 (s), 125.36 (s), 124.30 (d), 121.27 (d), 121.11 (d), 117.69 (s), 110.65 (d), 40.35 (CH₂), 29.87 (N-CH₃).

Analysis calculated for C₂₄H₂₂N₄O₆S₂·H₂O requires:

C, 52.9; H, 4.4; N, 10.3; S, 11.8%.

Found: C, 52.5; H, 4.5; N, 10.0; S, 11.2%.

10 Compound 113 of Table 1

Similar reaction of 2-chloro-1-methylindole-3-carboxylic acid [XXI] with SOCl₂ and N-methylaniline gave N-methyl-N-phenyl 2-chloro-1-methylindole-3-carboxamide [XXII: R₆ = Me; R₇ = Ph] (67% yield); mp (Me₂CO/water) 163°C.

¹H NMR ((CD₃)₂SO): δ 7.47 (1H, d, $J = 7.6$ Hz, H-4), 7.41 (1H, d, $J = 8.3$ Hz, H-7), 7.22-7.00 (7H, m, ArH), 3.63 (3H, s, N-CH₃), 3.42 (3H, s, N-CH₃).

¹³C NMR: δ 164.33 (CONMePh), 143.88 (s), 134.69 (s), 128.50 (d), 125.90 (d), 125.70 (d), 124.86 (s), 124.21 (s), 122.24 (d), 120.71 (d), 118.94 (d), 110.06 (d), 108.80 (s), 37.40 (N-CH₃), 29.77 (N-CH₃).

Analysis calculated for C₁₇H₁₅ClN₂O requires:

C, 68.3; H, 5.1; N, 9.4; Cl, 11.9%.

Found: C, 68.4; H, 5.1; N, 9.3; Cl, 12.1%.

Treatment of this with MeSLi as above gave 2,2'-dithiobis[N-methyl-N-phenyl-1-methylindolyl-3-carboxamide] (113) [V: R₁ = H, R₂ = CON(Me)Ph, R₃ = Me] (53% yield), mp 158-163°C.

¹H NMR ((CD₃)₂SO): δ 7.80 (1H, d, $J = 7.5$ Hz, H-4), 7.57 (1H, d, $J = 7.8$ Hz, H-7), 7.33-6.99 (7H, m, ArH), 3.86 (3H, s, N-CH₃), 3.33 (3H, s, N-CH₃).

¹³C NMR: δ 164.14 (CONMePh), 137.59 (s), 129.94 (s), 124.21 (s), 123.73 (s), 123.24 (d), 122.34 (d), 120.25

-149-

(d), 119.56 (d), 118.79 (d), 115.43 (s), 110.27 (d), 39.68 (N-CH₃), 30.99 (N-CH₃).

Analysis calculated for C₃₄H₃₁N₄S₂O₂ requires:

[M + H]⁺ 591.3447.

5 Found: [M + H]⁺ 591.3441 (FAB mass spectrum).

Analysis calculated for C₃₄H₃₀N₄S₂O₂ requires:

C, 69.1; H, 5.1; N, 9.5; S, 10.9%.

Found: C, 69.2; H, 5.2; N, 9.6; S, 10.6%.

10 Compound 114 of Table 1

Similar reaction of 2-chloro-1-methylindole-3-carboxylic acid [XXI] with SOCl₂ and 3-aminopropane-1,2-diol gave N-(2,3-dihydroxypropyl)-2-chloro-1-methylindole-3-carboxamide [XXII: R₆ = H; ,

15 R₇ = CH₂CH(OH)CH₂OH] (46%) as an oil.

¹H NMR ((CD₃)₂SO/D₂O): δ 7.94 (1H, d, J = 7.0 Hz, H-4), 7.53 (1H, d, J = 7.2 Hz, H-7), 7.38-7.19 (2H, m, H-5,6), 3.78 (3H, s, N-CH₃), 3.68-3.26 (5H, m, CH₂CHOHCH₂OH).

20 ¹³C NMR: δ 162.72 (CONH), 134.94 (s), 125.94 (s), 124.79 (s), 122.52 (d), 121.15 (d), 120.05 (d), 110.17 (d), 107.09 (d), 70.17 (CHOH), 63.90 (CH₂OH), 42.34 (CONHCH₂), 29.97 (N-CH₃).

Analysis calculated for C₁₃H₁₅ClN₂O₃ requires:

25 M⁺ 284.0742, 282.0771.

Found: M⁺ 284.0744, 282.0763 (mass spectrum).

Treatment of this with MeSLi as above gave 2,2'-dithiobis[N-(2,3-dihydroxypropyl)-1-methyl-indolyl-3-carboxamide] (114) [V: R₁ = H,

30 R₂ = CONHCH₂CH(OH)CH₂OH, R₃ = Me] (71% yield) as a yellow foam; mp 198°C (dec).

¹H NMR ((CD₃)₂SO/D₂O): δ 7.89 (1H, d, J = 8.1 Hz, H-4), 7.56 (1H, d, J = 8.4 Hz, H-7), 7.42 (1H, dd, J = 8.4, 7.3 Hz, H-6), 7.27 (1H, dd, J = 8.1, 7.3 Hz,

-150-

H-5), 3.75 (3H, s, N-CH₃), 3.40-3.20 (5H, m, CH₂CHOHCH₂OH).

¹³C NMR: δ 162.61 (CONH), 137.70 (s), 125.21 (s), 124.40 (d), 121.34 (d), 121.27 (d), 120.81 (s), 117.85 (s), 110.88 (d), 70.17 (CHOH), 63.75 (CH₂OH), 41.96 (CONHCH₂), 29.95 (N-CH₃).

Analysis calculated for C₂₆H₃₀N₄O₆S₂ requires:

C, 55.9; H, 5.4; N, 10.0; S, 11.5%.

Found: C, 55.4; H, 5.4; N, 9.7; S, 11.5%.

Compound 115 of Table 1

Similar reaction of 2-chloro-1-methylindole-3-carboxylic acid [XXI] with SOCl₂ and *N,N*-dimethylethylenediamine, followed by extraction into 3N HCl, neutralization with aqueous NH₃ and extraction with EtOAc gave *N,N*-dimethylaminoethyl-2-chloro-1-methylindole-3-carboxamide [XXII: R₆ = H, R₇ = CH₂CH₂NMe₂] as an oil (74% yield), which eventually solidified; mp 63°C.

¹H NMR (CDCl₃): δ 8.20 (1H, dd, *J* = 8.1, 1.7 Hz, H-4), 7.26-7.20 (3H, m, H-5,6,7), 7.01 (1H, br, CONH), 3.69 (3H, s, N-CH₃), 3.58 (2H, dt, *J* = 6.1, 5.1 Hz, CONHCH₂), 2.55 (2H, t, *J* = 6.1 Hz, CH₂N(CH₃)₂), 2.30 (6H, s, N(CH₃)₂).

¹³C NMR: δ 163.62 (CONH), 135.31 (s), 126.43 (s), 125.79 (s), 122.90 (d), 121.83 (d), 121.06 (d), 109.17 (d), 107.07 (s), 57.84 (CONHCH₂), 45.14 (N(CH₃)₂), 36.80 (CH₂N(CH₃)₂), 29.96 (N-CH₃).

Analysis calculated for C₁₄H₁₈ClN₃O requires:

M⁺ 281.1109, 279.1138.

Found: M⁺ 281.1106, 279.1118 (mass spectrum).

Following treatment of this with MeSLi as above, the reaction mixture was partitioned between CH₂Cl₂ and water. The organic portion was extracted with 3N HCl,

-151-

and the extract was neutralized with aqueous NH_3 ,
extracted with CH_2Cl_2 , and worked up to give an oil
which was dissolved in MeOH and allowed to stand at
20°C for 48 hours. The product was adsorbed directly
5 onto silica and chromatographed. Elution with
MeOH/EtOAc (1:19) containing a trace of concentrated
 NH_4OH gave 2,2'-dithiobis[N-(N,N-dimethylaminoethyl)
1-methylindolyl-3-carboxamide] (115) [V: $\text{R}_1 = \text{H}$,
 $\text{R}_2 = \text{CONHCH}_2\text{CH}_2\text{NMe}_2$, $\text{R}_3 = \text{Me}$] (54% yield);

10 mp (CH_2Cl_2 /light petroleum) 163.5-165°C.

^1H NMR (CDCl_3): δ 8.24 (1H, d, $J = 8.1$ Hz, H-7), 7.36
(1H, dd, $J = 8.2$, 7.8 Hz, H-6), 7.30 (1H, d,
 $J = 8.2$ Hz, H-7), 7.25 (1H, dd, $J = 8.1$, 7.8 Hz, H-5),
7.10 (1H, br, CONH), 3.60 (3H, s, N- CH_3), 2.99 (2H, dt,
15 $J = 6.3$, 5.5 Hz, CONHCH_2), 2.26 (2H, t, $J = 6.3$ Hz,
 $\text{CH}_2\text{N}(\text{CH}_3)_2$), 2.21 (6H, s, $\text{N}(\text{CH}_3)_2$).

^{13}C NMR: δ 163.71 (CONH), 138.27 (s), 126.64 (s),
125.20 (d), 122.70 (d), 122.11 (d), 118.46 (s), 110.08
(d), 57.72 (CONHCH_2), 45.19 ($\text{N}(\text{CH}_3)_2$), 36.81
20 ($\text{CH}_2\text{N}(\text{CH}_3)_2$), 30.15 (N- CH_3).

Analysis calculated for $\text{C}_{28}\text{H}_{36}\text{N}_6\text{O}_2\text{S}_2$ requires:

C, 60.8; H, 6.6; N, 15.2; S, 11.6%.

Found: C, 60.7; H, 6.8; N, 14.9; S, 11.4%.

25 Compound 116 of Table 1

Similar reaction of 2-chloro-1-methylindole-
3-carboxylic acid [XXI] with SOCl_2 and 4-aminopyridine
gave N-(4-pyridyl)-2-chloro-1-methylindole-

3-carboxamide [XXII: $\text{R}_6 = \text{H}$, $\text{R}_7 = 4\text{-pyridyl}$]

30 (61% yield); mp (CHCl_3 /light petroleum) 220-223°C.

^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 10.28 (1H, br, CONH), 8.47 (2H,
d, $J = 6.1$ Hz, H-2',6'), 7.82 (1H, d, $J = 7.5$ Hz,
H-4), 7.72 (2H, d, $J = 6.1$ Hz, H-3',5'), 7.63 (1H, d,
 $J = 8.0$ Hz, H-7), 7.33 (1H, dd, $J = 8.0$, 7.6 Hz, H-6),

-152-

7.25 (1H, dd, $J = 7.6, 7.5$ Hz, H-5), 3.84 (3H, s, N-CH₃).

¹³C NMR: δ 162.03 (CONH), 150.16 (d), 145.81 (s), 134.98 (s), 127.50 (s), 124.49 (s), 122.81 (d), 121.54 (d), 119.59 (d), 113.50 (d), 110.47 (d), 107.60 (s), 30.11 (N-CH₃).

Analysis calculated for C₁₅H₁₂ClN₃O requires:

C, 63.1; H, 4.2; N, 14.7%.

Found: C, 62.8; H, 3.9; N, 14.6%.

Reaction of this with MeSLi as above gave 2,2'-dithiobis[N-(4-pyridyl)-1-methylindolyl-3-carboxamide] (116) [V: R₁ = H, R₂ = CONH-4-pyridyl, R₃ = Me] (53% yield); mp 226-229°C (dec).

¹H NMR ((CD₃)₂SO): δ 14.46 (1H, s, CONH), 8.51 (2H, d, $J = 7.0$ Hz, H-2',6'), 8.13 (2H, d, $J = 7.0$ Hz, H-3',5'), 8.05 (1H, d, $J = 7.9$ Hz, H-4), 7.16 (1H, d, $J = 8.1$ Hz, H-7), 7.00 (2H, m, H-5,6), 3.68 (3H, s, N-CH₃).

¹³C NMR: δ 165.13 (s), 164.33 (CONH), 153.80 (s), 141.35 (d), 137.26 (s), 128.35 (s), 120.30 (d), 119.97 (d), 118.52 (d), 112.83 (d), 107.66 (d), 104.06 (s), 29.37 (N-CH₃).

Analysis calculated for C₃₀H₂₄N₆O₂S₂ requires:

C, 62.8; H, 4.4; N, 14.6; S, 11.2%.

Found: C, 62.4; H, 4.9; N, 14.5; S, 11.4%.

Compound 117 of Table 1

Similar reaction of 2-chloro-1-methylindole-3-carboxylic acid [XXI] with SOCl₂ and 3-aminopyridine gave N-(3-pyridyl)-2-chloro-1-methylindole-3-carboxamide [XXII: R₇ = H, R₈ = 3-pyridyl] (86% yield); mp (EtOAc/light petroleum) 175-177°C.

¹H NMR ((CD₃)₂SO): δ 10.13 (1H, s, CONH), 8.90 (1H, d, $J = 2.4$ Hz, H-2'), 8.30 (1H, dd, $J = 4.7, 1.4$ Hz,

-153-

H-6'), 8.18 (1H, ddd, $J = 4.5, 2.4, 1.4$ Hz, H-4'), 7.84 (1H, d, $J = 7.9$ Hz, H-4), 7.63 (1H, d, $J = 8.2$ Hz, H-7), 7.40 (1H, dd, $J = 4.7, 4.5$ Hz, H-5'), 7.32 (1H, dd, $J = 8.2, 7.7$ Hz, H-6), 7.25 (1H, dd, $J = 7.9, 7.7$ Hz, H-5), 3.84 (3H, s, N-CH₃).

¹³C NMR: δ 161.71 (CONH), 144.11 (d), 141.38 (d), 135.85 (s), 134.98 (s), 127.15 (s), 126.62 (d), 124.51 (s), 123.46 (d), 122.74 (d), 121.43 (d), 119.70 (d), 110.43 (d), 107.69 (s), 30.09 (N-CH₃).

Analysis calculated for C₁₅H₁₂ClN₃O requires:

C, 63.1; H, 4.1; N, 14.3; Cl, 13.6%.

Found: C, 63.2; H, 4.2; N, 14.9; Cl, 12.4%.

Treatment of this with MeSLi as above gave

2,2'-dithiobis[N-(3-pyridyl) 1-methylindolyl-

3-carboxamide] (117) [V: R₁ = H, R₂ = CONH-3-pyridyl, R₃ = Me] (71% yield); mp 257-260°C.

¹H NMR ((CD₃)₂SO): δ 13.82 (1H, s, CONH), 9.53 (1H, d, $J = 1.6$ Hz, H-2'), 8.44 (2H, m, H-4',6'), 8.05 (1H, d, $J = 8.0$ Hz, H-4), 7.91 (1H, dd, $J = 4.6, 4.5$ Hz, H-5'), 7.14 (1H, d, $J = 8.1$ Hz, H-7), 6.96 (2H, m, H-5',6'), 3.67 (3H, s, N-CH₃).

¹³C NMR: δ 164.76 (CONH), 162.70 (s), 140.01 (s), 136.97 (s), 134.17 (d), 132.51 (d), 131.06 (d), 128.44 (s), 127.08 (d), 119.90 (d), 119.45 (d), 118.39 (d), 107.50 (d), 103.89 (s), 29.25. (N-CH₃).

Analysis calculated for C₃₀H₂₄N₆O₂S₂ requires:

C, 63.8; H, 4.3; N, 14.9; S, 11.4%.

Found: C, 63.5; H, 4.9; N, 14.8; S, 11.1%.

30 Compound 118 of Table 1

Treatment of 2-chloro-1-methylindole-3-carboxamide

[XXII: R₇ = R₈ = H] (Andreani A, Rambaldi M, J. Het. Chem. 1988;25:1519-1523) with MeSLi as above gave 2,2'-dithiobis[1-methylindolyl-3-carboxamide] (118)

-154-

[V: $R_1 = H$, $R_2 = CONH_2$, $R_3 = Me$] (71% yield);

mp 186-188°C.

1H NMR ($(CD_3)_2SO$): δ 7.99 (1H, d, $J = 7.9$ Hz, H-4),
7.52 (1H, d, $J = 8.3$ Hz, H-7), 7.33 (1H, dd, $J = 8.3$,
5 7.2 Hz, H-6), 7.25-7.11 (3H, m, H-5 and $CONH_2$), 3.48
(3H, s, N- CH_3).

^{13}C NMR: δ 164.76 ($CONH_2$), 137.56 (s), 129.35 (s),
125.51 (s), 124.37 (d), 121.58 (d), 121.23 (d), 117.77
(s), 110.74 (d), 29.82 (N- CH_3).

10 Analysis calculated for $C_{20}H_{18}N_4O_2S_2 \cdot 0.5H_2O$ requires:

C, 57.3; H, 4.6; N, 13.4; S, 15.3%.

Found: C, 57.7; H, 4.5; N, 13.5; S, 15.4%.

Compound 119 of Table 1

15 Treatment of *N,N*-dimethyl 2-chloro-1-methylindole-
3-carboxamide [XXII: $R_7 = R_8 = Me$] (Bergman J,
Carlsson R, Sjöberg B, *J. Het. Chem.* 1977;14:1123-1134)
with MeSLi as above gave 2,2'-dithiobis[*N,N*-dimethyl-
1-methylindolyl-3-carboxamide] (119) [V: $R_1 = H$,
20 $R_2 = CONMe_2$, $R_3 = Me$]. Chromatography on silica gel,
eluting with EtOAc, followed by crystallization from
EtOAc/light petroleum gave pure material (54% yield);
mp 96-102°C.

1H NMR ($CDCl_3$): δ 7.43 (1H, d, $J = 8.0$ Hz, H-4), 7.31
25 (2H, m, H-6,7), 7.15 (1H, m, H-5), 3.64 (3H, s, N- CH_3),
2.91, 2.62 (2x3H, 2xbr, $N(CH_3)_2$).

^{13}C NMR: δ 165.89 ($CONMe_2$), 138.06 (s), 128.51 (s),
125.04 (s), 124.47 (d), 121.15 (d), 120.59 (d), 120.19
(s), 110.19 (d), 38.65 ($N(CH_3)_2$), 34.84 ($N(CH_3)_2$),
30 30.23 (N- CH_3).

Analysis calculated for $C_{24}H_{26}N_4O_2S_2 \cdot 0.5H_2O$ requires:

C, 60.6; H, 5.7; N, 11.7%.

Found: C, 60.3; H, 5.8; N, 11.2%.

-155-

Analysis calculated for $C_{24}H_{27}N_4S_2O_2$ requires:

$[M + H]^+$ 467.1575.

Found: $[M + H]^+$ 467.1559 (FAB mass spectrum).

5 Compound 120 of Table 1

10 A mixture of 2-chloroindole-3-carboxaldehyde
(7.0 g, 36 mmol) was reacted with a slight excess of
hydroxylamine hydrochloride and pyridine in refluxing
EtOH for 1 hour, to give the crude oxime (Latrell R,
Bartmann W, Musif J, Granzer E, German Patent
2,707,268, 31 Aug 1978, Chem. Abstr. 1978;89:179858y).
A solution of this in Ac_2O (100 mL) was heated under
reflux for 1 hour, cooled, and stirred with water
(700 mL). The precipitated solid was collected, washed
15 with water, and crystallized from aqueous MeOH to give
2-chloro-1H-indole-3-carbonitrile (3.7 g, 58%);
mp 177-180°C.

20 1H NMR ($(CD_3)_2SO$): δ 13.23 (1H, s, NH), 7.60 (1H, d,
 $J = 7.5$ Hz, ArH), 7.50 (1H, d, $J = 7.9$ Hz, ArH), 7.34
(1H, t, $J = 7.5$ Hz, ArH), 7.29 (1H, t, $J = 7.3$ Hz, ArH).
 ^{13}C NMR: δ 134.0, 131.5, 126.2, 114.1 (C), 123.8,
122.3, 117.9, 112.3 (CH), 83.8 (CN).

Analysis calculated for $C_9H_5ClN_2$ requires:

C, 61.2; H, 2.9; N, 15.9%.

25 Found: C, 61.2; H, 2.7; N, 15.9%.

30 A solution of the above nitrile (2.5 g, 14 mmol)
in Me_2CO was treated with a slight excess of MeI and
 K_2CO_3 under reflux for 1 hour. Crystallization of the
crude product from hexane gave 2-chloro-1-methylindole-
3-carbonitrile (1.88 g, 70%); mp 112-114°C.

1H NMR ($CDCl_3$): δ 7.61-7.55 (1H, m, ArH), 7.34-7.21
(3H, m, ArH), 3.74 (3H, s, CH_3).

^{13}C NMR: δ 135.0, 133.4, 126.0, 114.1 (C), 123.9,
122.7, 118.8, 110.1 (CH), 85.2 (CN).

-156-

Analysis calculated for $C_{10}H_7ClN_2$ requires:

C, 63.0; H, 3.7; N, 14.7%.

Found: C, 63.0; H, 3.6; N, 14.7%.

5 Treatment of this with MeSLi as above gave 2,2'-
dithiobis(2-chloro-1-methylindole-3-carbonitrile) (120)

[V: $R_1 = H$, $R_2 = CN$, $R_3 = Me$] (53% yield);

mp 205-207°C.

10 1H NMR ($(CD_3)_2SO$): δ 7.69 (1H, d, $J = 8.3$ Hz, H-4),
7.51 (1H, d, $J = 8.0$ Hz, H-7), 7.42 (1H, dd, $J = 8.0$,
7.3 Hz, H-6), 7.28 (1H, dd, $J = 8.3$, 7.3 Hz, H-5), 3.82
(3H, s, N-CH₃).

Analysis calculated for $C_{20}H_{14}N_4S_2$ requires:

C, 64.2; H, 3.8; N, 15.0; S, 17.1%.

Found: C, 64.2; H, 3.8; N, 15.1; S, 17.7%.

15

Compound 121 of Table 1

3-Acetyl-2-chloro-1-methylindole was prepared by
the reported method (Coppola GM, Hardtmann GE, J. Het.
Chem. 1977;14:117-1118). This was reacted with MeSLi
20 as above gave 3-acetyl-1-methyl-2-indolinethione
[XV: $R_5 = Me$] (66% yield); mp 180°C.

1H NMR ($(CD_3)_2SO$): δ 15.60 (1H, br, SH), 7.64 (1H, d,
 $J = 6.5$ Hz, H-4), 7.39 (1H, d, $J = 7.6$ Hz, H-7), 7.32
(1H, dd, $J = 7.6$, 7.3 Hz, H-6), 7.24 (1H, dd, $J = 7.3$,
25 6.5 Hz, H-5), 3.65 (3H, s, N-CH₃), 2.66 (3H, s, COCH₃).

^{13}C NMR: δ 178.29 (COCH₃), 140.56 (s), 125.21 (d),
124.67 (s), 123.27 (d), 120.60 (d), 111.31 (s), 109.99
(d), 29.31 (N-CH₃), 22.44 (COCH₃).

Analysis calculated for $C_9H_5ClN_2$ requires:

30 C, 61.2; H, 2.9; N, 15.9%.

Found: C, 61.2; H, 2.7; N, 15.9%.

A solution of the above thione (0.10 g, 0.49 mmol)
in MeOH/EtOAc (1:9) (10 mL) was stirred vigorously with
30% H₂O₂ (0.20 mL) for 4 hours. The solution was

-157-

concentrated to a volume of 0.5 mL, and the orange precipitate was filtered off and washed well with MeOH to give 2,2'-dithiobis(3-acetyl-1-methylindole) (121) [V: $R_1 = H$, $R_2 = COMe$, $R_3 = Me$] (100% yield);

mp 178.5-179.5°C.

1H NMR ($(CD_3)_2SO$): δ 8.14 (1H, d, $J = 8.1$ Hz, H-4), 7.62 (1H, d, $J = 8.3$ Hz, H-7), 7.39 (1H, dd, $J = 8.3$, 7.3 Hz, H-6), 7.27 (1H, dd, $J = 8.1$, 7.3 Hz, H-5), 3.75 (3H, s, N-CH₃), 2.00 (3H, s, COCH₃).

^{13}C NMR: δ 192.56 (COCH₃), 137.65 (s), 133.73 (s), 125.41 (s), 124.79 (d), 122.73 (d), 121.95 (d), 121.43 (s), 110.92 (d), 30.34 (COCH₃), 29.43 (N-CH₃).

Analysis calculated for $C_{22}H_{20}N_2O_2S_2 \cdot 0.5H_2O$ requires:

C, 63.3; H, 5.1; N, 6.7%.

Found: C, 63.7; H, 4.7; N, 6.8%.

Compound 122 of Table 1

Similar reaction of 2-chloro-1-methylindole-3-carboxylic acid [XXI] with $SOCl_2$ and 2-aminopyridine gave *N*-(2'-pyridyl)-2-chloro-1-methylindole-3-carboxamide [XXII: $R_6 = H$, $R_7 = 2$ -pyridyl] (42% yield); mp (light petroleum) 123°C.

1H NMR ($CDCl_3$): δ 8.85 (1H, s, CONH), 8.41 (1H, d, $J = 8.4$ Hz, H-4), 8.30 (2H, m), 7.72 (1H, m), 7.28 (3H, m), 7.02 (1H, dd, $J = 7.2$, 4.9 Hz), 3.74 (3H, s, N-CH₃).

^{13}C NMR: δ 161.58 (CONH), 151.85 (s), 147.92 (d), 138.27 (d), 135.46 (s), 127.22 (s), 125.84 (s), 123.45 (d), 122.48 (d), 121.16 (d), 119.47 (d), 114.25 (d), 109.44 (d), 106.59 (s), 30.21 (N-CH₃).

Analysis calculated for $C_{15}H_{12}ClN_3O$ requires:

C, 63.1; H, 4.2; N, 14.7%.

Found: C, 62.9; H, 4.2; N, 14.4%.

-158-

Treatment of this with MeSLi as above gave
2,2'-dithiobis[N-(2'-pyridyl)-1-methylindole-
3-carboxamide] (122) [V: $R_1 = H$, $R_2 = \text{CONH-2-pyridyl}$,
 $R_3 = \text{Me}$] (68% yield); mp 270-272°C (dec).

5 ^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 14.93 (1H, br, CONH), 8.32 (1H, d, $J = 6.0$ Hz), 8.25 (1H, dd, $J = 8.3$, 7.7 Hz), 8.02 (1H, dd, $J = 7.4$, 3.7 Hz), 7.57 (1H, d, $J = 8.7$ Hz), 7.35 (1H, t, $J = 6.6$ Hz), 7.21 (1H, dd, $J = 5.1$, 3.0 Hz), 7.04 (2H, m), 3.69 (3H, s, N-CH₃).

10 ^{13}C NMR: δ 166.48 (s), 165.41 (CONH), 149.16 (s), 145.34 (d), 137.66 (s), 137.49 (s), 127.89 (s), 120.66 (d), 120.44 (d), 118.32 (d), 117.55 (d), 115.32 (d), 107.96 (d), 102.69 (s), 29.40 (N-CH₃).

Analysis calculated for $\text{C}_{30}\text{H}_{24}\text{N}_6\text{O}_2\text{S}_2 \cdot 0.25\text{H}_2\text{O}$ requires:

15 C, 63.3; H, 4.3; N, 14.8; S, 11.3%.

Found: C, 63.2; H, 4.5; N, 14.8; S, 11.7%.

Compound 123 of Table 1

Similar treatment of 1-methyl-2-indolinethione
20 [IV: $R_1, R_2 = H$, $R_3 = \text{CH}_3$] with the acyl azide derived from 2-furoic acid gave 3-(2-furoyl)-1-methyl-2-indolinethione [IV: $R_1 = H$, $R_2 = \text{CO(2-furyl)}$; $R_3 = \text{Me}$] (85% yield); mp 113.5°C.

25 ^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 15.90 (1H, br, SH), 8.28 (1H, d, $J = 1.6$ Hz, H-5'), 7.97 (1H, d, $J = 8.0$ Hz, H-4), 7.56 (1H, d, $J = 3.6$ Hz, H-3'), 7.46 (1H, d, $J = 8.0$ Hz, H-7), 7.37 (1H, dd, $J = 8.0$, 7.4 Hz, H-6), 7.21 (1H, dd, $J = 8.0$, 7.4 Hz, H-5), 6.94 (1H, dd, $J = 3.6$, 1.6 Hz, H-4'), 3.72 (3H, s, N-CH₃).

30 ^{13}C NMR: δ 180.09 (CS), 160.65 (CO), 147.95 (d), 147.27 (s), 140.92 (s), 126.05 (d), 123.26 (s), 123.12 (d), 121.04 (d), 119.19 (d), 113.22 (d), 110.11 (d), 109.64 (s), 29.79 (N-CH₃).

-159-

Analysis calculated for $C_{14}H_{11}NO_2S$ requires:

C, 65.3; H, 4.4; N, 5.7; S, 12.7%.

Found: C, 65.4; H, 4.3; N, 5.4; S, 12.5%.

Reaction of the above compound with I_2 as described above gave 2,2'-dithiobis[3-(2-furoyl)-1-methylindole] (123) [V: $R_1 = H$; $R_2 = CO(2-furyl)$; $R_3 = Me$] (85% yield); mp 175-176.5°C.

1H NMR ($CDCl_3$): δ 7.47 (1H, d, $J = 8.1$ Hz, H-4), 7.33 (1H, dd, $J = 1.6, 0.7$ Hz, H-5'), 7.23 (1H, dd, $J = 8.1, 7.8$ Hz, H-6), 7.21 (1H, d, $J = 8.1$ Hz, H-7), 7.09 (1H, dd, $J = 8.1, 7.9$ Hz, H-5), 6.63 (1H, dd, $J = 3.6, 0.7$ Hz, H-3'), 6.23 (1H, dd, $J = 3.6, 1.6$ Hz, H-4'), 3.73 (3H, s, NCH_3).

^{13}C NMR: δ 177.09 (CO), 152.55 (s), 145.91 (d), 138.18, 131.32, 125.80 (3xs), 124.72 (d), 123.60 (s), 121.73, 121.12, 119.16, 111.91, 110.06 (5xd), 30.54 (NCH_3).

Analysis calculated for $C_{28}H_{20}N_2O_4S_2 \cdot 0.5H_2O$ requires:

Found: C, 64.4; H, 4.1; N, 5.4; S, 12.3%.

C, 64.7; H, 4.1; N, 5.6; S, 12.4%.

Compound 124 of Table 1

Similar treatment of 1-methyl-2-indolinethione [IV: $R_1, R_2 = H$, $R_3 = CH_3$] with the isocyanate derived from thiophene-2-carboxylic acid gave 2,2'-dithiobis[N-(2-thienyl)-1-methylindole-3-carboxamide] (124) [V: $R_1 = H$, $R_2 = CONHfuryl$, $R_3 = Me$] (21% yield; mp 183°C (dec)).

1H NMR ($(CD_3)_2SO$): δ 11.26 (1H, s, CONH), 7.93 (1H, d, $J = 8.0$ Hz, H-4), 7.62 (1H, d, $J = 8.3$ Hz, H-7), 7.34 (1H, dd, $J = 8.3, 7.4$ Hz, H-6), 7.24 (1H, dd, $J = 8.0, 7.4$ Hz, H-5), 7.05 (1H, dd, $J = 5.3, 3.6$ Hz, H-4'), 6.94 (1H, d, $J = 5.3$ Hz, H-5'), 6.41 (1H, d, $J = 3.6$ Hz, H-3'), 3.95 (3H, s, NCH_3).

-160-

^{13}C NMR: δ 160.10 (CONH), 139.86 (s), 137.81 (s), 136.86 (s), 125.19 (s), 123.96 (d), 123.69 (d), 121.28 (d), 120.54 (d), 116.85 (d), 114.73 (s), 111.20 (d), 110.77 (d), 30.54 (N-CH₃).

5 Analysis calculated for C₂₈H₂₂N₄O₂S₄·H₂O requires:

C, 57.6; H, 4.0; N, 9.6%.

Found: C, 57.6; H, 4.1; N, 10.0%.

EXAMPLE J

10 Preparation of Compound 125 of Table 1 by the Method
Outlined in Scheme 9

Reaction of 3-chlorocarbonyl-1-(phenylsulfonyl)-
indole [XXIII] (Ketcha DM, Gribble GW, J. Org. Chem.

1985;50:5451-5457) with an excess of benzylamine in

15 CH₂Cl₂) (method of Ketcha and Gribble) gave

N-benzyl-1-(phenylsulfonyl)indole-3-carboxamide [XXIV:
R₈ = CH₂Ph]; mp (MeOH) 188-189°C.

^1H NMR (CDCl₃): δ 8.05 (1H, s, H-2), 8.03-7.86 (4H, m,
ArH), 7.56-7.26 (10H, m, ArH), 6.43 (1H, m, NH), 4.64

20 (2H, d, *J* = 5.7 Hz, CH₂).

Analysis calculated for C₂₂H₁₈N₂O₃S requires:

C, 67.7; H, 4.5; N, 7.2; S, 8.2%.

Found: C, 67.4; H, 4.8; N, 7.1; S, 8.2%.

A solution of the above *N*-benzyl-1-(phenyl-

25 sulfonyl)indole-3-carboxamide [XXIV: R₈ = CH₂Ph]

(4.2 g, 11 mmol) in dry THF (200 mL) was treated at

-78°C with a solution of 2.5 M *n*-BuLi in hexanes

(9.1 mL, 23 mmol), and the stirred mixture was allowed

to warm to -20°C for 15 minutes, before being recooled

30 to -78°C, when it was treated with methyldisulfide

(2.5 mL, 28 mmol). The mixture was allowed to warm to

20°C, then quenched with water (25 mL). Volatiles were

removed under reduced pressure, and the residue was

extracted with EtOAc. Workup of the organic layer gave

-161-

a crude product. This was dissolved in MeOH (300 mL), mixed with a solution of K_2CO_3 (6.9 g, 50 mmol) in water (125 mL), and heated under gentle reflux under N_2 for 2 hours to ensure complete hydrolysis of the phenylsulfonyl group (J. Org. Chem. 1985;50:5451-5457).

MeOH was removed under reduced pressure, and the residue was diluted with water and extracted with CH_2Cl_2 . Chromatography of the resulting oil on Al_2O_3 (eluting with CH_2Cl_2) gave *N*-benzyl-2-(methylthio)-indole-3-carboxamide [XXV: $R_8 = CH_2Ph$] (2.8 g, 88% yield) as an oil.

1H NMR ($CDCl_3$): δ 10.65 (1H, s, H-1), 8.29 (d, $J = 5.1$ Hz, H-4), 7.87 (1H, t, $J = 5.6$ Hz, CONH), 7.34-7.08 (8H, m, ArH), 4.73 (2H, d, $J = 5.6$ Hz, CH_2), 2.33 (3H, s, SMe).

^{13}C NMR ($CDCl_3$): δ 165.6 (C=O), 138.5, 136.4, 133.1 and 110.8 (C), 128.5, 127.2, 127.1, 122.9, 121.4, 126.8 and 111.2 (CH), 43.2 (CH_2), 18.5 (CH_3).

HREIMS calculated for $C_{17}H_{16}N_2OS$:

296.0983.

Found: 296.0985.

A solution of the above *N*-benzyl-2-(methylthio)-indole-3-carboxamide [XXV: $R = CH_2Ph$] (0.85 g, 2.87 mmol) in DMA (5 mL) was added under N_2 to a stirred suspension of MeSLi (0.93 g, 17.2 mmol) in DMA (10 mL). After warming at 80°C for 6 hours, the mixture was acidified with 3N HCl, extracted with CH_2Cl_2 , and worked up. Traces of DMA were removed under high vacuum, and the residue was dissolved in MeOH (15 mL) and treated dropwise with H_2O_2 (0.5 mL of 30% solution). After chilling at -30°C overnight, the precipitate was filtered off to give 2,2'-dithiobis[*N*-benzylindolyl-3-carboxamide] (125) [V: $R_1 = R_3 = H$, $R_2 = CONHCH_2Ph$], (74%); mp 203-205°C.

-162-

¹H NMR ((CD₃)₂SO): δ 12.97 (1H, s, NH), 8.48 (1H, t, J = 5.7 Hz, CONHCH₂), 7.86 (1H, d, J = 8.2 Hz, H-4), 7.40 (2H, d, J = 8.3 Hz, H-2',6'), 7.34 (3H, dd, J = 8.3, 8.2 Hz, H-7,3',5'), 7.25 (1H, t, J = 8.2 Hz, H-4'), 7.20-7.10 (2H, m, H-5,6), 4.56 (2H, d, J = 5.7 Hz, CONHCH₂).

¹³C NMR: δ 164.71 (CONH), 139.77 (s), 136.69 (s), 135.30 (s), 128.16 (d), 127.15 (d), 126.56 (d), 124.44 (s), 122.63 (d), 120.78 (d), 119.25 (d), 111.60 (d), 110.54 (s), 42.62 (CONHCH₂).

Analysis calculated for C₃₂N₂₆N₄O₂S₂ requires:

C, 68.3; H, 4.7; N, 10.0; S, 11.4%.

Found: C, 68.0; H, 4.8; N, 9.9; S, 11.2%.

15 Compound 126 of Table 1

Reaction of 3-chlorocarbonyl-1-(phenylsulfonyl)-indole [XXIII] with an excess of aniline as above gave N-phenyl-1-(phenylsulfonyl)indole-3-carboxamide [XXIV: R₈ = Ph]; mp (MeOH) 220-222.5°C.

20 ¹H NMR: δ (CDCl₃) 8.18 (1H, s, H-2), 8.12 (1H, d, J = 7.8 Hz, H-4), 7.99 (1H, d, J = 8.3 Hz, H-7), 7.91 (2H, d, J = 7.9 Hz, ArH), 7.90 (1H, m, NH), 7.65 (2H, d, J = 8.4 Hz, ArH), 7.57 (1H, t, J = 7.8 Hz, ArH), 7.45 (2H, t, J = 7.8 Hz, ArH), 7.41-7.33 (4H, m, ArH), 7.15 (1H, t, J = 7.4 Hz, H-5).

25 Analysis calculated for C₂₁H₁₈N₂O₃S requires:

C, 67.0; H, 4.3; N, 7.4; S, 8.5%.

Found: C, 66.9; H, 4.4; N, 7.3; S, 8.5%.

30 Treatment of this with n-BuLi/methyldisulfide as above gave 2-(methylthio)-N-phenylindole-3-carboxamide [XXV: R₈ = Ph] (81%) as an oil.

¹H NMR (CDCl₃): δ 10.19 (1H, s, H-1), 9.59 (1H, s, CONH), 8.47 (1H, d, J = 6.8 Hz, H-4), 7.80 (2H, d,

-163-

$J = 8.5$ Hz, ArH), 7.43-7.35 (3H, m, ArH), 7.28-7.16 (3H, m, ArH), 2.51 (3H, s, SCH₃).

¹³C NMR (CDCl₃): δ 163.5 (CO), 138.2, 136.1, 132.5, 127.3, 111.2 (CH), 19.1 (CH₃).

5 HREIMS calculated for C₁₆H₁₄N₂OS:

282.0827

Found: 282.0827.

Treatment of this with MeSLi as above gave

2,2'-dithiobis[N-phenylindolyl-3-carboxamide] (126)

10 [V: R₁ = R₃ = H, R₂ = CONHPh], (67%); mp 220-223°C.

¹H NMR ((CD₃)₂SO): δ 12.73 (1H, s, NH), 9.88 (1H, s, CONH), 7.81 (1H, d, $J = 7.9$ Hz, H-4), 7.69 (2H, d, $J = 8.4$ Hz, H-2',6'), 7.46 (1H, d, $J = 7.7$ Hz, H-7), 7.34 (2H, dd, $J = 8.4, 8.3$ Hz, H-3',5'), 7.24 (1H, dd, $J = 7.7, 7.7$ Hz, H-6), 7.17 (1H, dd, $J = 7.9, 7.7$ Hz, H-5), 7.10 (1H, dd, $J = 8.3$ Hz, H-4').

15 ¹³C NMR: δ 163.27 (CONH), 138.89 (s), 136.73 (s), 133.94 (s), 128.53 (d), 125.12 (s), 123.49 (d), 123.17 (d), 120.99 (d), 120.32 (d), 119.97 (d), 112.89 (s), 20 111.67 (d).

Analysis calculated for C₃₀H₂₂N₄O₂S₂ requires:

C, 67.4; H, 4.2; N, 10.5; S, 12.0%.

Found: C, 67.1; H, 4.3; N, 10.6; S, 12.0%.

25 Compound 127 of Table 1

Reaction of 3-chlorocarbonyl-1-(phenylsulfonyl)-indole [XXIII] with an excess of methylamine as above gave N-methyl-1-(phenylsulfonyl)indole-3-carboxamide [XXIV: R_g = Me]; mp (MeOH) 192.5-195°C.

30 ¹H NMR (CDCl₃): δ 8.06 (1H, s, H-2), 8.03-7.84 (4H, m, ArH) 7.53-7.26 (5H, m, ArH), 6.37 (1H, m, NH), 2.99 (d, $J = 4.9$ Hz, CH₃).

-164-

Analysis calculated for $C_{16}H_{14}N_2O_3S$ requires:

C, 61.1, H, 4.5; N, 8.9; S, 10.2%.

Found: C, 61.1; H, 4.7; N, 8.9; S, 10.0%.

5 Treatment of this with *n*-BuLi/methyldisulfide as
above gave *N*-methyl-2-(methylthio)indole-3-carboxamide
[XXV: $R_8 = \text{Me}$] (95%); mp (hexane- CH_2Cl_2)
138.5-139.5°C.

10 ^1H NMR (CDCl_3): δ 10.31 (1H, s, H-1), 8.35-8.26 (1H,
m, H-4), 7.44 (1H, t, $J = 4.8$ Hz, NH), 7.38-7.30 (1H,
m, ArH), 7.19-7.11 (2H, m, ArH), 3.06 (3H, d,
 $J = 4.8$ Hz, CH_3), 2.49 (3H, s, SCH_3).

^{13}C NMR (CDCl_3): δ 166.4 (CO), 136.4, 132.4, 127.4 and
111.7 (C), 123.1, 121.5, 121.2, 111.1 (CH), 26.3 and
18.9 (CH_3).

15 Analysis calculated for $C_{11}H_{12}N_2OS$ requires:

C, 60.0; H, 5.5; N, 12.7; S, 14.6%.

Found: C, 59.8; H, 5.7; N, 12.7; S, 14.5%.

20 Treatment of this with MeSLi as above gave
2,2'-dithiobis[*N*-methylindolyl-3-carboxamide] (127)
[V: $R_1 = R_3 = \text{H}$, $R_2 = \text{CONHMe}$], (57% yield);
mp 232-236°C (dec).

25 ^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 12.94 (1H, s, NH), 7.85 (1H, br,
CONH), 7.81 (1H, d, $J = 8.0$ Hz, H-4), 7.46 (1H, d,
 $J = 8.0$ Hz, H-7), 7.20 (1H, dd, $J = 8.0$, 7.7 Hz, H-6),
7.14 (1H, dd, $J = 8.0$, 7.7 Hz, H-5), 2.88 (3H, d,
 $J = 4.5$ Hz, CONHCH_3).

^{13}H NMR: δ 165.20 (CONH), 136.70 (s), 134.76 (s),
124.47 (s), 122.61 (d), 120.71 (d), 119.55 (d), 111.55
(d), 111.02 (s), 26.22 (CONHCH_3).

30 Analysis calculated for $C_{20}H_{18}N_4O_2S_2$ requires:

C, 58.5; H, 4.4; N, 13.7; S, 15.6%.

Found: C, 58.4; H, 4.7; N, 13.6; S, 15.4%.

-165-

Compound 128 of Table 1

A solution of 2-(methylthio)-*N*-phenyl-1*H*-indole-3-carboxamide [XXV: $R_8 = H$] (1.8 g, 6.4 mmol) in EtOH (400 mL) was treated with 3-(dimethylamino)propyl chloride hydrochloride (10.0 g, 64 mmol) and K_2CO_3 (13 g, 96 mmol) and heated under reflux for 3 hours. A further 10 equivalents of the reagents were then added, and the mixture was heated under reflux for a further 48 hours. EtOH was removed under reduced pressure, and the residue was diluted with water to give crude product. This was chromatographed on alumina, eluting with CH_2Cl_2 containing 0.2% MeOH, to give 1-[3-(dimethylamino)propyl]-2-(methylthio)-*N*-phenyl-1*H*-indole-3-carboxamide [XXVI: $R_8 = H$, $R_9 = (CH_2)_3NMe_2$] (0.49 g, 21%) as an oil.

1H NMR ($CDCl_3$): δ 9.93 (1H, s, NH), 8.54 (1H, d, $J = 7.8$ Hz, H-4), 7.74 (2H, d, $J = 8.6$ Hz, H-2',6'), 7.42-7.24 (5H, m, ArH), 7.11 (1H, t, $J = 7.4$ Hz, ArH), 4.46 (2H, t, $J = 7.4$ Hz, 1- CH_2), 2.47 (3H, s, SCH_3), 2.37 (2H, t, $J = 6.9$ Hz, CH_2N), 2.27 (6H, s, $N(CH_3)_2$), 1.97 (2H, dxt, $J = 7.4$, 6.9 Hz, $CH_2CH_2CH_2$).
 ^{13}C NMR: δ 162.6 (CO), 138.8, 136.7, 131.4, 127.5, 114.1 (C), 129.0, 124.1, 123.7, 122.8, 122.1, 119.8, 110.0 (CH), 56.5, 42.0, 28.3 (CH_2), 45.3 ($N(CH_3)_2$), 21.1 (SCH_3).

Analysis calculated for $C_{21}H_{25}N_3O_2$ requires:

$$[M + H^+] = 368.1797.$$

HRFABMS Found: $[M + H^+] = 368.1812$.

This was treated with MeSLi at 80°C for 8 hours as above. Water was added, the mixture was washed with CH_2Cl_2 , and the aqueous portion was carefully neutralized with 3N HCl and extracted with CH_2Cl_2 . This extract was worked up to give an oil which was dissolved in MeOH and treated dropwise at room

-166-

temperature with a saturated solution of I_2 in CH_2Cl_2 until no starting material was evident on TLC analysis. The reaction mixture was absorbed directly onto silica and chromatographed. MeOH/EtOAc (1:9) eluted foreruns, while MeOH/EtOAc (1:9) containing a trace of concentrated NH_4OH gave 2,2'-dithiobis[1-{3-(dimethyl-amino)}propyl]-N-phenyl-1H-indole-3-carboxamide] (128) [V: $R_1 = H$, $R_2 = CONHPh$, $R_3 = (CH_2)_3NMe_2$] (10% yield) as a yellow foam.

1H NMR (CD_3OD): δ 8.19 (1H, d, $J = 7.3$ Hz, H-4), 7.64 (1H, d, $J = 7.5$ Hz, H-7), 7.30-7.20 (3H, m, ArH), 7.10-6.95 (4H, m, ArH), 4.41 (2H, t, $J = 6.2$ Hz, CH_2N), 2.74 (2H, t, $J = 6.7$ Hz, CH_2NMe_2), 2.64 (6H, s, $N(CH_3)_2$), 2.09 (2H, m, $CH_2CH_2CH_2$).

Analysis calculated for $C_{40}H_{45}N_6O_2S_2$ requires:

$$[M + H^+] = 705.3045.$$

HRFABMS found: $[M + H^+] = 705.3035.$

EXAMPLE K

Preparation of Compound 129 of Table 1 by the Method Outlined in Scheme 10

To a stirred 25°C solution of 41 mL (558 mmol) of DMF and 75 mL of dichloromethane was added dropwise a solution of 133.5 g (465 mmol) of $POBr_3$ in 100 mL of dichloromethane at such a rate to maintain a gentle reflux via the exothermic reaction (ca. 1 hour). The resulting thick tan suspension was stirred vigorously for 10 minutes, then treated dropwise over 20 minutes with a solution of 27.38 g (186 mmol) of 1-methyl-2-indolinone [VII: $R_1 = H$, $R_3 = CH_3$] in 55 mL of dichloromethane. The mixture was heated at reflux for 3.5 hours, cooled to 25°C, and the supernatant was decanted and concentrated to a thick reddish brown oil. This was combined with the solids above and treated

-167-

very cautiously with portionwise addition of ca. 20 g of ice, then with 112 g of 50% (w/w) aqueous NaOH, all the while keeping the temperature between 30-40°C (pH = 3). An additional 20 g of 50% NaOH, then 100 mL of ice water were added, and the precipitate was collected by filtration. The solids were washed well with water, then dried over P₂O₅ to leave 42.6 g of crude bromoaldehyde; mp 92-97°C. The solids were dissolved in ca. 65 mL of dichloromethane and the solution filtered over 165 g of flash silica gel placed in a 600 mL sintered glass funnel. The frit was washed with dichloromethane until all the product had eluted. The combined product fractions were concentrated to leave 34.66 g (78%) of nearly pure 2-bromo-1-methylindole-3-carboxaldehyde [XXVI: R₁ = H, R₃ = CH₃, X = Br]; mp 110-112° which was used directly in the next reaction.

To a vigorously stirred solution of 2.38 g (10 mmol) of 2-bromo-1-methylindole-3-carboxaldehyde [XXVI: R₁ = H, R₃ = CH₃, X = Br], 10 mL of 2-methyl-2-butene, and 40 mL of p-dioxane at 25°C was added dropwise over ca. 15 minutes a solution of 5 g (55 mmol) of sodium chlorite and 5 g (36 mmol) of NaH₂PO₄·H₂O in 25 mL of water. The solution was maintained at 25°C. After 3.5 hours, the mixture was treated with an additional 2.5 g each of the chlorite and phosphate. After a total reaction time of 24 hours, the mixture was extracted 3 times with dichloromethane, then the aqueous phase was acidified to pH 2 with aqueous HCl, and extracted once more. The combined organic extracts were washed with water, dried, and evaporated to leave a solid residue that was boiled in 2-propanol. After cooling, the solids were collected by filtration, washed with a little

-168-

2-propanol, and dried to leave 2.21 g (87%) of 2-bromo-1-methylindole-3-carboxylic acid [XXVII: $R_1 = H$, $R_3 = CH_3$, $X = Br$] as a beige solid; mp ca. 198°C (dec), in 2 crops.

5 A suspension of 2.54 g (10 mmol) of 2-bromo-1-methylindole-3-carboxylic acid [XXVII: $R_1 = H$, $R_3 = CH_3$, $X = Br$], 2.54 g (10 mmol) of bis(2-oxo-3-oxazolidinyl)phosphinic chloride, 2.78 mL (20 mmol) of triethylamine, and 25 mL of
10 1,2-dichloroethane was heated at reflux for 1.5 hours. The mixture was cooled and poured into 150 mL 5% aqueous sodium bicarbonate solution and stirred for 30 minutes. The mixture was extracted with
15 dichloromethane (3 times), the combined organic phase washed with water, brine, dried ($MgSO_4$), and concentrated to leave a red oil. The oil was trituated in ethyl acetate:hexanes and the solids were collected by filtration to give 0.95 g of a side
20 product; mp 227-228°C (dec). The filtrate was concentrated to a viscous oil that was dissolved into chloroform and adsorbed into 9 g of flash SiO_2 . This was introduced onto a column containing flash SiO_2 and the column was eluted with hexanes:ethyl acetate (95:5). Product fractions were pooled, concentrated,
25 and trituated from isooctane to give 1.96 g (63%) of 2-bromo-1-methylindole-3-carboxylic acid, t-butyl ester [XXVIII: $R_1 = H$, $R_2 = COO$ -t-butyl, $R_3 = CH_3$] as a white solid; mp 87-88°C.

Analysis calculated for $C_{14}H_{16}BrNO_2$ requires:

30 C, 54.21; H, 5.20; N, 4.52; Br, 25.76%.

Found: C, 54.28; H, 5.20; N, 4.49, Br, 25.83%.

An ice-cold suspension of 119 mg (1.5 mmol) of elemental selenium in 2 mL of THF under N_2 was treated dropwise with 1.1 mL of methyl lithium:lithium bromide

-169-

complex (1.5 M in ether). The flask was opened to the air and with a brisk stream of N_2 , the resultant white suspension was warmed to ca. 85°C to distill off the ether and most of the THF. The residual semi-solid was cooled in an ice bath and diluted with 1.5 mL of DMA followed by 155 mg (0.5 mmol) of 2-bromo-1-methylindole-3-carboxylic acid, t-butyl ester. The resultant solution was stirred at room temperature for 24 hours, cooled to 0°C, then treated with 2 mL of dilute acetic acid. The mixture was diluted with water and extracted with chloroform (3 x 10 mL). The combined extracts were washed with water (4 times), dried (Na_2SO_4), and concentrated to leave a golden solid. The solid was suspended in 2.3 mL of 2:1 v/v HOAc:H₂O and the suspension was treated with 154 mg of $NaBO_3 \cdot 4H_2O$, then stirred at 25°C for 30 minutes. The solids were collected by filtration, washed with water, and dried to leave 119 mg (77 %) of 2,2'-diselenobis[1-methyl-1H-indole-3-carboxylic acid, t-butyl ester] (129) [XXIX: $R_1 = H$, $R_2 = COO-t-butyl$, $R_3 = CH_3$]; mp 187-189°C.

1H NMR ($CDCl_3$): δ 8.13 (1H, dd, $J = 0.7, 7.9$ Hz, H-4), 7.31-7.19 (3H, m, ArH), 3.63 (3H, s, NCH_3), 1.44 (9H, s, $C(CH_3)_3$).

Analysis calculated for $C_{28}H_{32}N_2O_4Se_2 \cdot 0.2H_2O$ requires:
C, 54.06; H, 5.25; N, 4.50%.
Found: C, 54.40; H, 5.48; N, 4.11%.

Compound 130 of Table 1

To an ice-cold solution of 4 mL of trifluoroacetic acid under nitrogen was added 420 mg (0.68 mmol) of 2,2'-diselenobis[1-methyl-1H-indole-3-carboxylic acid, t-butyl ester] (101) [XXIX: $R_1 = H$, $R_2 = COO-t-butyl$, $R_3 = CH_3$]. The suspension was maintained at 0°C for

-170-

3 hours, then poured into ice water. The solids were collected by filtration, washed well with water, and dried to leave 361 mg of product; mp 165°C (dec). The solids were suspended into 80 mL 10% aqueous NH_4OH and the insolubles were removed by filtration. The filtrate was adjusted to pH 3 with 6N aqueous HCl , and the precipitated solids were collected by filtration, washed with water, and dried to leave 268 mg (78%) of 2,2'-diselenobis[1-methyl-1H-indole-3-carboxylic acid] (130) [XXIX: $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{COOH}$, $\text{R}_3 = \text{CH}_3$]; mp 174°C (dec) as an orange solid.

^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 12.35 (1H, s, CO_2H), 8.04 (1H, d, $J = 7.9$ Hz, H-4), 7.56 (1H, d, $J = 8.4$ Hz, H-7), 7.31-7.20 (2H, m, ArH), 3.63 (3H, s, NCH_3).

Analysis calculated for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_4\text{Se}_2 \cdot 0.1\text{H}_2\text{O}$ requires:
C, 47.28; H, 3.21; N, 5.51%.
Found: C, 47.20; H, 3.20; N, 5.12%.

Compound 131 of Table 1

A 25°C suspension of 2.79 g (11 mmol) of 2-bromo-1-methylindole-3-carboxylic acid [XXVII: $\text{R}_1 = \text{H}$, $\text{R}_3 = \text{CH}_3$, $\text{X} = \text{Br}$] in 13 mL of 1,2-dichloroethane was treated dropwise with 2.41 mL (33 mmol) of thionyl chloride. The mixture was heated at 75°C for 2 hours. The solution was concentrated to a solid which was co-evaporated once with dichloromethane. The solid was ice-cooled and treated rapidly with 26 mL of 40% aqueous methylamine. The bath was removed and the suspension was stirred at 25°C for 2 hours. The solids were collected by filtration, washed well with water, and dried at 200 mm/70°C/12 hours over P_2O_5 to leave 2.2 g (75%) of product; mp 154-157°C.

Recrystallization from MeOH provided 1.91 g of pure 2-bromo-1-methylindol-3-N-methylcarboxamide

-171-

[XXX: $R_1 = H$, $R_3 = CH_3$, $R_7 = H$, $R_8 = CH_3$] as a beige solid; mp 159-160°C in three crops.

An ice-cold solution of lithium methyl selenide in 2 mL of DMA, made up as previously described from 237 mg (3 mmol) of elemental Se and 2.2 mL of methylolithium (1.5 M in ether) in 3 mL of THF, was treated with 267 mg (1.0 mmol) of 2-bromo-1-methylindole-3-N-methylcarboxamide [XXX: $R_1 = H$, $R_3 = CH_3$, $R_7 = H$, $R_8 = CH_3$]. The resultant solution was stirred at room temperature for 3.5 hours, cooled to 0°C, then treated with 5% aqueous HCl. The mixture was extracted with dichloromethane (2 x 10 mL), the combined extracts washed with water (2 times), then concentrated in vacuo to leave an oil that was dissolved in methanol. The solution was ice-cooled and treated with 113 μ L of 30% aqueous H_2O_2 . After stirring for 10 minutes, the resultant suspension was filtered, and the solids were washed with 2-propanol and dried to leave 183 mg (67%) of 2,2'-diselenobis [N,1-dimethyl-1H-indole-3-carboxamide] (131) [XXIX: $R_1 = H$, $R_2 = CONHCH_3$, $R_3 = CH_3$] as a yellow solid; mp 225-230°C (dec). 1H NMR ($CDCl_3 + (CD_3)_2SO$): δ 7.97 (1H, d, $J = 7.9$ Hz, H-4), 7.39-7.18 (3H, m, ArH), 6.84 (1H, s, $NHCH_3$), 3.85 (3H, s, indole NCH_3), 2.12 (3H, d, $J = 4.5$ Hz, $NHCH_3$). Analysis calculated for $C_{22}H_{22}N_4O_2Se_2 \cdot 0.9H_2O$ requires: C, 48.17; H, 4.37; N, 10.21%. Found: C, 48.20; H, 4.22; N, 10.28%.

30 Compound 132 of Table 1

Similar reaction of 2-chloro-1-methylindole-3-carboxylic acid [XXVII: $R_1 = H$, $R_3 = CH_3$, $X = Cl$] with $SOCl_2$ as described in Example I and reaction of this with 3 equivalents of N,N-diethylethylenediamine

-172-

in dichloromethane at 0°C followed by workup gave 2-chloro-1-methylindole-3-N-(2-(diethylamino)ethyl)-carboxamide [XXX: $R_1 = H$, $R_6 = H$, $R_7 = (CH_2)_2NEt_2$, $X = Cl$] as a soft solid in 68% yield, used without further purification.

Treatment of this with lithium methyl selenide as described above gave 2,2'-diselenobis[N-[2-(diethylamino)ethyl]-1-methyl-1H-indole-3-carboxamide] (132) [XXIX: $R_1 = H$, $R_2 = CONH(CH_2)_2NEt_2$, $R_3 = CH_3$] (68% yield); mp 128-130°C. Reaction of the free base with excess hydrogen chloride in 2-propanol followed by concentration to an oil and crystallization at 25°C gave the compound as a dihydrochloride salt (18% yield); mp 160-164°C.

1H NMR ($(CD_3)_2SO$): δ 10.13 (1H, s, $^+NH(CH_2CH_3)_2$), 8.14-8.11 (1H, m, $CONH$), 7.89 (1H, d, $J = 8.2$ Hz, H-4), 7.57 (1H, d, $J = 8.4$ Hz, H-7), 7.34-7.17 (2H, m, ArH), 3.63 (3H, s, NCH_3), 3.17-3.14 (2H, m, $CONHCH_2$), 3.06-3.00 (4H, m, $N(CH_2CH_3)_2$), 2.86 (2H, t, $J = 6.5$ Hz, $CONHCH_2CH_2$), 1.16 (6H, t, $J = 7.2$ Hz, $N(CH_2CH_3)_2$). Analysis calculated for $C_{32}H_{44}N_6O_2Se_2 \cdot 2.0HCl \cdot 1.7H_2O$ requires:

C, 47.67; H, 6.18; N, 10.42; Cl^- , 8.79%.

Found: C, 47.71; H, 6.12; N, 10.35; Cl^- , 8.97%.

Compound 133 of Table 1

A mechanically stirred suspension of 15 g (83.5 mmol) of 2-chloroindole-3-carboxaldehyde [XXVI: $R_1 = R_3 = H$, $X = Cl$] (Schule, et al., Arch. Pharm. [Weinheim] 1972;305:523-533), 84 mL of 2-methyl-2-butene, and 200 mL of p-dioxane in an ice bath was treated with a solution of 40 g each of sodium chlorite and sodium dihydrogen phosphate monohydrate in 200 mL of water. The biphasic mixture was then stirred

-173-

vigorously at 25°C for 3.5 hours. An additional 16 g each of solid sodium chlorite and sodium dihydrogen phosphate monohydrate was added and the mixture was stirred for another 3.5 hours. The mixture was diluted with 350 mL of ethyl acetate and 200 mL of water. The layers were separated and the aqueous phase was extracted with 300 mL of ethyl acetate. The combined organic extracts were extracted with cold 2% aqueous NaOH (3 x 200 mL). The basic extracts were combined and acidified to pH 4 with 6N aqueous HCl. The precipitated solids were collected by filtration, washed well with water, and air dried overnight. The solids were dissolved in 150 mL of hot acetone and the solution was treated with 65 mL of hexane. After storage at 3°C for 20 hours, the solids were collected by filtration, washed with cold acetone, and dried to leave 7.71 g of pure 2-chloroindole-3-carboxylic acid [XXVII: $R_1 = R_3 = H$, $X = Cl$] as an off-white solid; mp 181.5°C (dec). Further processing of the filtrate as above afforded 2.41 g of a second crop; mp 179.5°C (dec). Total yield 10.12 g (62%).

The acid chloride of 2-chloroindole-3-carboxylic acid [XXVII: $R_1 = R_3 = H$, $X = Cl$] was made via $SOCl_2$ as described above. Reaction of this with a saturated solution of anhydrous methylamine in THF at 0°C gave 2-chloroindole-3-N-methylcarboxamide [XXX: $R_1 = R_3 = H$, $R_6 = H$, $R_7 = CH_3$, $X = Cl$]; mp 234-236°C, in 51% yield.

Reaction of this with lithium methyl selenide as described above gave 2,2'-diselenobis[N-methyl-1H-indole-3-carboxamide] (133) [XXIX: $R_1 = R_3 = H$, $R_3 = CONHCH_3$] (20% yield), mp 272-275°C (decomp). 1H NMR ($(CD_3)_2SO$): δ 12.36 (1H, s, indole NH), 7.83 (1H, d, $J = 7.7$ Hz, H-4), 7.79 (1H, d, $J = 4.1$, $NHCH_3$),

-174-

7.48 (1H, d, $J = 7.7$ Hz, H-7), 7.16-7.07 (2H, m, ArH),
2.90 (3H, d, $J = 4.1$ Hz, NHCH_3).

Analysis calculated for $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_2\text{Se}_2 \cdot 0.9\text{H}_2\text{O}$ requires:

C, 46.15; H, 3.83; N, 10.76%.

5 Found: C, 46.08; H, 3.44; N, 10.45%.

Compound 134 of Table 1

The acid chloride of 2-chloroindole-3-carboxylic acid [XXVII: $R_1 = R_3 = \text{H}$, $X = \text{Cl}$] was made via SOCl_2
10 as described above. Reaction of this with
3 equivalents of N,N -diethylethylenediamine in ether as
described above followed by workup gave 2-chloroindole-
3- N -(2-(diethylamino)ethyl)carboxamide [XXX:
 $R_1 = R_3 = R_6 = \text{H}$, $R_7 = (\text{CH}_2)\text{NET}_2$, $X = \text{Cl}$]; mp $99-108^\circ\text{C}$
15 in 38% yield.

^1H NMR (CDCl_3): δ 11.50 (1H, s, indole NH), 8.19 (1H,
d, $J = 6.5$ Hz, H-4), 7.33 (1H, d, $J = 8.4$ Hz, H-7),
7.21-7.15 (3H, m, ArH and CONH), 3.54 (2H, q,
 $J = 5.3$ Hz, CONHCH_2), 2.69 (2H, t, $J = 6.0$ Hz,
20 $\text{CONHCH}_2\text{CH}_2$), 2.59 (4H, q, $J = 7.2$ Hz, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.05
(6H, t, $J = 7.2$ Hz, $\text{N}(\text{CH}_2\text{CH}_3)_2$).

Reaction of this with lithium methyl selenide as
described above gave 2,2'-diselenobis[N -(2-(diethyl-
amino)ethyl)-1H-indole-3-carboxamide] (134) [XXIX:
25 $R_1 = R_3 = \text{H}$, $R_2 = \text{CONH}(\text{CH}_2)_2\text{NET}_2$] (44% yield);
mp $225-226^\circ\text{C}$ (dec). Salt formation as above gave the
compound as the dihydrochloride salt (85% yield);
mp $257-259^\circ\text{C}$ (dec).

^1H NMR ($(\text{CD}_3)_2\text{SO}$): δ 12.75 (1H, s, indole NH), 10.08
30 (1H, s, $^*\text{NH}(\text{CH}_2\text{CH}_3)_2$), 8.09 (1H, t, $J = 5.7$ Hz, CONH),
7.93 (1H, d, $J = 8.9$ Hz, H-4), 7.51 (1H, d, $J = 6.8$ Hz,
H-7), 7.19-7.12 (2H, m, ArH), 3.78-3.73 (2H, m,
 CONHCH_2), 3.32 (2H, t, $J = 6.5$ Hz, $\text{CONHCH}_2\text{CH}_2$),

-175-

3.29-3.20 (4H, m, $N(CH_2CH_3)_2$), 1.26 (6H, t, $J = 7.2$ Hz, $N(CH_2CH_3)_2$).

Analysis calculated for $C_{30}H_{40}N_6O_2Se_2 \cdot 2.0HCl \cdot 1.0H_2O$ requires:

5 C, 47.07; H, 5.79; N, 10.98; Cl^- , 9.26%.

Found: C, 47.01; H, 5.70; N, 10.56; Cl^- , 8.87%.

Compound 135 of Table 1

A mixture of 2.09 g (10 mmol) of 2-chloroindole-3-N-methylcarboxamide [XXX: $R_1 = R_3 = R_6 = H$, $R_7 = CH_3$, $X = Cl$], 1.72 g (10 mmol) of 2-diethylaminoethyl chloride hydrochloride ($n = 2$, $Q = Cl$, $R_8 = R_9 = Et$), 7.5 g (23 mmol) of anhydrous cesium carbonate, 3 g of activated 3A molecular sieves, and 20 mL of acetone was stirred under nitrogen at 25°C for 16 hours. The mixture was filtered over celite and the filtrate was concentrated to a solid that was partitioned between chloroform and water. The organic phase was dried (Na_2SO_4) and concentrated to a residue that was crystallized from ethyl acetate:hexanes (5:8). The solids were collected and dried to leave 1.43 g of 2-chloro-1-[2-(diethylamino)ethyl]-N-methyl-1H-indole-3-carboxamide [XXX: $R_1 = R_6 = H$, $R_3 = (CH_2)_2NEt_2$, $R_7 = CH_3$, $X = Cl$]; mp 103-104°C, in 46% yield.

1H NMR ($CDCl_3$): δ 8.24 (1H, d, $J = 8.0$ Hz, H-4), 7.33-7.21 (3H, m, ArH), 6.35 (1H, s, $CONHCH_3$), 4.27 (2H, t, $J = 7.6$ Hz, 1- NCH_2), 3.06 (3H, d, $J = 4.8$ Hz, $CONHCH_3$), 2.73 (2H, t, $J = 7.5$ Hz, 1- $NHCH_2CH_2$), 2.62-2.55 (4H, m, $N(CH_2CH_3)_2$), 1.02 (6H, t, $J = 7.0$ Hz, $N(CH_2CH_3)_2$).

Reaction of this with lithium methyl selenide as described above gave 2,2'-diselenobis[1-[2-(diethylamino)ethyl]-N-methyl-1H-indole-3-carboxamide] (135)

-176-

[XXIX: $R_1 = H$, $R_2 = CONHCH_3$, $R_3 = (CH_2)_2NEt_2$] (63% yield); mp 156-157°C.

Analysis calculated for $C_{32}H_{44}N_6O_2Se_2 \cdot 0.5H_2O$ requires:

C, 54.01; H, 6.37; N, 11.81%.

5 Found: C, 54.14; H, 6.23; N, 11.54%.

EXAMPLE L

Preparation of Compound 136 of Table 1 by the method outlined in Scheme 11.

10 An ice-cold solution of 15 g (50 mmol) of the N-trifluoroacetamide of D-tryptophan, synthesized by methods previously outlined (J. Org. Chem. 1979;44:2805-2807) in 50 mL of THF under N_2 was treated sequentially with 7.1 g (52.5 mmol) of 1-hydroxybenzo-
15 triazole then 10.83 g (52.5 mmol) of 1,3-dicyclohexylcarbodiimide. After 15 minutes, the solution was treated with 5.74 mL (52.6 mmol) of benzylamine. The solution was maintained at 0-5°C for 1 hour, then let warm to 25°C overnight. The mixture was filtered and
20 the collected solids were washed with ethyl acetate. The filtrate was concentrated to an oil that was dissolved in 250 mL of ethyl acetate. The solution was washed sequentially with 250 mL portions of 10% aqueous acetic acid, water, 5% aqueous sodium hydrogen
25 carbonate, water and brine, then dried ($NaSO_4$), and concentrated to a solid. Crystallization from 170 mL of 65:35 2-propanol:petroleum ether afforded 12.81 g (66%) of (R)-N-(phenylmethyl)- α -[(trifluoroacetyl)-amino]-1H-indole-3-propanamide [II: $R_1 = H$, $R_2 =$
30 $CH_2CH(NHCOCF_3)CONHCH_2Ph$, $R_3 = H$] as an off-white solid which was used directly in the next reaction; mp 186-188°C.

To an ice-cold solution of 10 g (25.7 mmol) of (R)-N-(phenylmethyl)- α -[(trifluoroacetyl)amino]-

-177-

1H-indole-3-propanamide [XXIX: $R_1 = H$, $R_2 = CH_2CH(NHCOCF_3)CONHCH_2Ph$, $R_3 = H$] in 70 mL of THF was added dropwise Se_2Cl_2 . The resultant deep red suspension was stirred at 0-5°C for 4 hours, then
5 quenched with 300 mL of water. The solids were collected by filtration, washed well with water, and air dried to leave 12 g of impure product as an orange solid. A portion of this material (10.7 g) was dissolved in 100 mL of methanol and the solution under
10 N_2 was cooled in an ice bath. Sodium borohydride (ca 1 g) was added portionwise until there was no more color discharge. The mixture was poured immediately into a N_2 purged separatory funnel containing 200 mL of ether. The mixture was diluted with 200 mL of water,
15 the mixture shaken, and the phases separated. The aqueous layer was treated with a small portion of additional sodium borohydride, extracted again with ether, ice-cooled, then acidified to pH 1 with concentrated HCl. The aqueous phase was extracted
20 twice with ethyl acetate, then the combined extracts were dried ($MgSO_4$) and filtered through a pad of flash silica gel. The filtrate was concentrated to leave 5.91 g of a foam that was dissolved in ca 40 mL of absolute ethanol. The solution was kept at 25°C for
25 several hours to initiate crystallization, then stored at 5°C. The solids were collected by filtration, washed with 2-propanol, and dried to leave 4.23 g of pure [R-(R*,R*)]-2,2'-diselenobis[N-(phenylmethyl)- α -[(trifluoroacetyl)amino]-1H-indole-3-propanamide]
30 [XXIX: $R_1 = H$, $R_2 = CH_2CH(NHCOCF_3)CONHCH_2Ph$, $R_3 = H$], as a yellow powdery solid; mp 181-185°C.
Analysis calculated for $C_{40}H_{34}N_6O_4F_6Se_2 \cdot H_2O$ requires:
C, 50.43; H, 3.81; N, 8.82%.
Found: C, 50.47; H, 3.57; N, 8.71%.

-178-

Further processing of the filtrate by chromatography over flash SiO₂, eluting first with dichloromethane then 7% ethyl acetate in dichloromethane, provided an additional 671 mg of product following crystallization; mp 180-183°C.

A suspension of 233.5 mg (0.25 mmol) of this diselenide in 4.5 mL of dry absolute ethanol was treated with 95 mg (2.5 mmol) of sodium borohydride. The mixture was heated at reflux for 15 minutes, then treated with 95 mg of additional borohydride. The mixture was refluxed for 1.25 hours, then treated with a third 95 mg portion of borohydride. After refluxing for 30 minutes, the mixture was cooled to 25°C, diluted with methanol, and poured into an ice-cold stirring mixture of 6N HCl and ethyl acetate. The resultant mixture was stirred vigorously for 15 minutes, filtered, the phases separated, and the aqueous layer extracted once more with ethyl acetate. The combined ethyl acetate phases were then back extracted with 5% aq HCl (five times). The acidic aqueous layers were combined and diluted with an equal volume of ethyl acetate. While carefully monitoring the pH, the stirred solution was treated carefully with 10% aqueous NaOH until pH = 9.5. The resultant yellow precipitate was collected by filtration, washed well with water, and dried to leave 90 mg of [R-(R*,R*)]-2,2'-diselenobis[α-amino-N-(phenylmethyl)-1H-indole-3-propanamide] (136) [XXIX: R₁ = H, R₂ = CH₂CH(NH₂)CONHCH₂Ph, R₃ = H], as a yellow powder; mp 172-174°C.

¹H NMR ((CD₃)₂SO): δ 11.62 (1H, s, NH), 8.23 (1H, t, J = 5.1 Hz, NHCH₂), 7.61 (1H, d, J = 8.0 Hz, ArH), 7.38 (1H, d, J = 8.2 Hz, ArH), 7.35-6.95 (7H, m, ArH), 4.20, 4.17 (2x1H, 2xdd, J = 15.2, 5.8 Hz, NHCH₂), 3.46-3.40

-179-

(1H, br m, Ar-CH₂CH), 3.04-2.98 (1H, br m, Ar-CH),
2.75-2.68 (1H, br m, Ar-CH), 1.70 (2H, br s, NH₂).
Analysis calculated for C₃₆H₃₆N₆O₂Se₂·1.5H₂O requires:
C, 56.18; H, 5.11; N, 10.68%.

5 Found: C, 55.91; H, 4.72; N, 10.68%.

Processing of the ethyl acetate layer from the
base treatment provided 15 mg of additional product;
mp 165-171°C. Total yield = 105 mg (57%).

10 Compound 137 of Table 1

Starting from the *N*-trifluoroacetamide of
L-tryptophan (*J. Org. Chem.* 1979;44:2805-2807) and
following the same procedures as outlined for the
synthesis of compound 136 of Table 1, there was
15 obtained [S-(R*,R*)]-2,2'-diselenobis[α-amino-
N-(phenylmethyl)-1*H*-indole-3-propanamide] (137)
[XXIX: R₁ = H, R₂ = CH₂CH(NH₂)CONHCH₂Ph, R₃ = H] as a
yellow powder; mp 171°C (dec).

20

BIOLOGICAL AND BIOCHEMICAL EFFECTS

Tyrosine Kinase Inhibition Assay and Growth Inhibition
Effects on Cells in Tissue Culture

25 Table 2 provides representative data on inhibition
of the epidermal growth factor receptor tyrosine
kinase, and on cell growth inhibition.

In Table 2: No. is the compound number as
recorded in Table 1.

30 IC₅₀ (EGFR TK) is the concentration of drug
necessary to reduce incorporation of P³² in GAT by 50%.

IC₅₀ (PDGFR TK) is the concentration of drug
necessary to reduce incorporation of P³² in Glu-Tyr by
50%.

-180-

IC₅₀ growth Inhibition is (cell growth inhibition) is the concentration of drug necessary to reduce the cellular growth rate by 50%.

5

TABLE 2. IC₅₀ Data for EGRF-R and PDGF-R Inhibition and Cell Growth Inhibition for Selected Compounds of Table 1

No.	IC ₅₀ (μ M) or % Inhibition at 100 μ M		Growth Inhibition
	EGRF-R	PDGF-R	
1	14.9	--	
2	26%	--	
3	43%	8.6%	
4	27%	--	
5	4%	--	
6	25	8.5%	
7	1.3	--	94
8	8.5	--	
9	52%	--	16
10	10%	--	34

-181-

TABLE 2 (cont'd)

No.	IC ₅₀ (μ M) or % Inhibition at 100 μ M		Growth Inhibition
	EGRF-R	PDGF-R	
5	11	24%	--
	12	3%	--
	13	43%	--
	14	22	--
	15	6.8	--
10	16	23	--
	17	12.5%	--
	18	2%	9%
	19	10%	--
	20	9	--
15	21	1.0	64
	22	--	--
	23	--	--
	24	19%	--
	25	8.7	--
20	26	23%	5%
	27	17.8	--
	28	33	--
	29	8.3	--
	30	9.3	--
25	31	35.5	--
	32	34.5	4.7%
	33	39	16.7%
	34	38	12.8%
	35	16.5	33.9%
30	36	4.8	--
	37	3.3	--
	38	36.5%	--
	39	20.6	--
	40	16.3%	--
35	41	8.4	--
	42	26%	--
	43	2.9	--
	44	16.6%	5%
	45	1.6	--
40	46	11.4%	--
	47	0.85	--
	48	35.5	--

-182-

TABLE 2 (cont'd)			
No.	IC ₅₀ (μ M) or % Inhibition at 100 μ M		Growth Inhibition
	EGRF-R	PDGF-R	
5	49	84.1	--
	50	16.0	62.6%
	51	7.0	--
	52	68.2	18.3%
	53	4.2	--
10	54	29	20.6%
	55	44	--
	56	7.3	44.5%
	57	46%	14.5%
	58	68%	--
15	59	30.5	11.4%
	60	53%	--
	61	37%	11%
	62	6.0	71%
	63	60	--
20	64	29	--
	65	17.8	--
	66	8.3	--
	67	18%	2%
	68	14%	--
25	69	55.6%	8.9%
	70	8.6	1%
	71	20%	5%
	72	47%	22%
	73	4.3	21%
30	74	23%	--
	75	6%	3%
	76	7%	19%
	77	9%	1%
	78	27%	7%
35	79	11%	20%
	80	0%	16%
	81	3.6	2%
	82	6.5	--
	83	22.3	57%
40	84	35%	22%
	85	8%	7%
	86	4.9	5%

-183-

TABLE 2 (cont'd)			
No.	IC ₅₀ (μ M) or % Inhibition at 100 μ M		Growth Inhibition
	EGRF-R	PDGF-R	
5	87	34%	44%
	88	54	51%
	89	11.4	3%
	90	26	36.5
	91	5.2	--
10	92	--	--
	93	30%	--
	94	--	--
	95	9.4	--
	96	--	--
15	97	10.1	28.1 1.8
	98	1.5	9% 5-12
	99	40	19% 2.8
	100	18%	23%
	101	5.5	--
20	102	6.1	--
	103	7%	-- 3.8
	104	20%	--
	105	16.9	33%
	106	34%	--
25	107	12.0	--
	108	20%	--
	109	47	8%
	110	13	--
	111	5.3	76%
30	112	10.0	69%
	113	5%	29%
	114	42.9	7.0
	115	26	19.7 >50
	116	4%	7.9
35	117	25%	4.2
	118	4.7	78%
	119	21.2	73%
	120	6.9	--
	121	5.6	--
40	122	51%	--
	123	--	--
	124	--	--

-184-

TABLE 2 (cont'd)

No.	IC ₅₀ (μM) or % Inhibition at 100 μM		Growth Inhibition
	EGRF-R	PDGF-R	
125	78%	--	
126	60%	--	
5 127	6.8	--	
128	--	--	
129	31%	--	
130	3.5	--	
131	5.8	--	5.5
10 132	4.7	--	20
133	13.0	--	<5
134	4.6	--	8
135	6.9		
136			
15 137			

EGF Receptor Tyrosine Kinase Assay

20 Membrane vesicles were prepared by the method described in Cohen S, Ushiro H, Stoscheck C, and Chinkers M. A native 170,000 epidermal growth factor receptor-kinase complex from shed plasma membrane vesicles, J. Biol. Chem. 1982;257:1523-1531, and kept

25 frozen at -90°C until use. At the time of assay, membranes were solubilized in 4% Triton X-100 and 10% glycerol. The reaction is carried out in wells of a 96-well microtiter plate in a total volume of 125 L. Buffer containing 20 mM Hepes (pH 7.4), 15 mM MgCl₂,

30 4 mM MnCl₂, and 0.02% BSA followed by 5 to 20 mg of membrane protein and 150 ng of epidermal growth factor. The plates are incubated for 10 minutes at room temperature to activate the receptor kinase. 20 g of GAT (random polymer of glycine, alanine, and

35 tyrosine) and 0.2 mCi of α-[P³²] ATP plus or minus

-185-

compound are added and incubated 10 minutes at room temperature. The reaction is stopped by addition of 125 mL of 30% TCA, precipitate washed twice with 200 mL of 15% TCA on 0.65 micron filters, and the filters counted by scintillation spectrometry.

PDGF Receptor Tyrosine Kinase Inhibition Assay

Recombinant baculovirus containing human PDGF β receptor intracellular tyrosine kinase domain was used to infect SF9 cells to overexpress the protein, and cell lysates were used for the assay. The ability of the tyrosine kinase to phosphorylate glutamate - tyrosine substrate in the presence of P^{32} -ATP and inhibitor was measured by counting the incorporation of P^{32} in Glu-Tyr in TCA precipitable material.

Table 2 provides representative data on inhibition of the PDGF receptor tyrosine kinase. In Table 2, No. refers to the compound number as recorded in Table 1.

DETAILED STUDIES ON THE BIOLOGICAL EFFECTS OF COMPOUNDS 21 AND 70

Effects on Cells in Tissue Culture

Swiss 3T3 fibroblasts, that were growth arrested in serum-free media for 24 hours, were exposed to various concentrations of compound for 2 hours. The cells were then exposed to individual growth factors for 5 minutes and proteins that were phosphorylated on tyrosine in response to the mitogens and were detected by Western blotting techniques using phosphotyrosine antibodies. Similar techniques were used for tumor cell lines except the time in serum-free media was increased.

-186-

At concentrations of 10 to 50 mM, Compound 21 suppressed: (1) EGF mediated phosphorylation of a variety of endogenous proteins; (2) PDGF mediated autophosphorylation of the PDGF receptor as well as PDGF mediated tyrosine phosphorylation of other endogenous proteins and; (3) bFGF mediated tyrosine phosphorylation. 70 was more selective and inhibited only bFGF mediated tyrosine phosphorylation and at concentrations as low as 2 mM.

Effects on Growth Factor Mediated Mitogenesis

Swiss 3T3 fibroblasts, that were growth arrested in serum-free media for 24 hours, were exposed to various concentrations of compound for 2 hours. The cells were then exposed to individual growth factors for 24 hours and mitogenesis assessed by measuring tritiated thymidine incorporation into DNA.

The concentration of 21 and 70 required to inhibit growth factor mediated mitogenesis by 50% for the following growth factors was as follows:

Growth Factor	IC ₅₀ (μM) for 21	IC ₅₀ (μM) for 70
EGF	2	3
PDGF	8	4
bFGF	13	3
serum	19	3

Growth Inhibition Assay

Swiss 3T3 mouse fibroblasts were maintained in DMEM/F12 media containing 10% fetal calf serum. Two mL of cells at a density of 1×10^4 /mL were placed in 24-well plates plus or minus various concentrations of

-187-

the inhibitor. The cells were grown at 37°C under 5% CO₂ for 72 hours and then counted by Coulter counter. The data were expressed as the concentration of inhibitor necessary to decrease the growth rate by 50%.

5 Compound 21 was growth inhibitory for a variety of human tumor cell lines as well as the Swiss 3T3 fibroblasts. The concentration of 21 necessary to inhibit cell growth by 50% is shown below:

10

Cell Line	IC ₅₀ (μM)
MDA 468 breast	43
A431 epidermoid	62
A549 lung	30
15 MDV-7 breast	39
MDA-231 breast	15
Swiss 3T3 fibroblasts	64
HT-29 colon	55

20

Although the carboxyl containing structures are among the most active enzyme inhibitors, they are poorly transported into the cell, whereas the less
25 active esters are transported efficiently and once in the cytoplasm rendered highly active by esterases. Esters may, therefore, be more favorable than carboxylic acids in this invention.

30 The data of Table 2 show that the 2-thioindoles of general Formula I listed in Table 1 include compounds which are active as potent inhibitors of protein tyrosine kinases and as cytotoxic agents.

35 The invention is not limited to the particular embodiments shown and described herein, since various changes and modifications may be made without departing

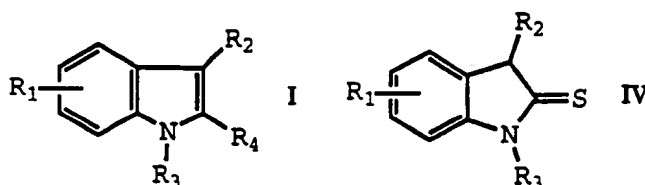
-188-

from the spirit and scope of the invention as defined
by the following claims.

-189-

CLAIMS

1. 2-Thioindole, 2-indolinethione and polysulfide compounds of the group represented by the general Formulas I and IV



10 and pharmaceutically acceptable salts thereof, wherein

R_1 is a member selected from H, halogen, R, OH, OCOR, OR, CF_3 , NO_2 , NH_2 , NHR , $COOH$, $CONHR$, $(CH_2)_nOH$, $(CH_2)_nOR$, $(CH_2)_nNH_2$, $(CH_2)_nNHR$, and $(CH_2)_nNRR$, and further represents replacement in the ring of 1 or 2 ring methine ($-CH=$) atoms with aza ($-N=$) atoms;

R_2 is a member selected from

C_{2-4} alkyl,

$(CH_2)_nCOOH$,

$(CH_2)_nCOOR$,

$(CH_2)_nCOR$,

$(CH_2)_nSO_2R$,

$(CH_2)_nSO_2NRR$,

$(CH_2)_nSO_2NHR$,

$CH=CHCOOH$,

$(CH_2)_nCH-COOH$,
|
OH

$(CH_2)_nCH-COOH$,
|
NH₂

$(CH_2)_nCONH_2$,

$(CH_2)_nCONHR$,

30

-190-

35 (CH₂)_nCONRR,
(CH₂)_nCONHCH₂Ph,
CONHR,
CONRR,
CONHPh,
40 COY,
COPhCOOH,
COPhCOOR,
(CH₂)_nCONHPh,
(CH₂)_nCONHPhR,
45 SO₂Y;

n is an integer from 1 to 4;

R is lower alkyl;

R₃ is a member selected from H, lower alkyl,
and benzyl;

50 Y represents a benzene, pyridine, thiophene,
furan, thiazole, or imidazole ring optionally
substituted with a lower alkyl, COOH, OH, OCOR,
NH₂, CONHR, CONRR, OR, or NHR group; and

R₄ represents SH, S_oX, and S_oQ where o is
55 1, 2, or 3, X is a member selected from H, lower
alkyl, benzyl, and benzene, pyridine, thiophene,
furan, thiazole, and imidazole rings, and Q is
another 2-thioindolyl moiety of Formula I provided
that the group does not comprise compounds having
60 the names

2-(2-thioxo-3-indolinyl)acetic acid,
2-(1-methyl-2-thioxo-3-indolinyl)acetic acid,
methyl 2-(2-thioxo-3-indolinyl)acetate,
ethyl 2-(1-methyl-2-thioxo-3-indolinyl)-
65 acetate,
bis[methylindolinyl-3-acetate-(2)]disulfide,
bis[indolyl-3-acetic acid-(2)]disulfide,

-191-

bis[methylindolyl-3-acetate-(2)]trisulfide,
and
bis[1-methylindolyl-3-acetic acid-(2)]-
disulfide.

2. A thioindole compound according to Claim 1
selected from

methyl 2-(1-methyl-2-thioxo-3-indoliny)-
acetate,

N-benzyl (2-thioxo-3-indoliny)acetamide,
3-(2-thioxo-3-indoliny)propanoic acid,
3-(1-methyl-2-thioxo-3-indoliny)propanoic
acid,

methyl 3-(2-thioxo-3-indoliny)propanoate,
ethyl 3-(2-thioxo-3-indoliny)propanoate,
3-(1-methyl-2-thioxo-3-indoliny)propanoate,
ethyl 3-(1-methyl-2-thioxo-3-indoliny)-
propanoate,

N-benzyl 3-(2-thioxo-3-indoliny)propanamide,
4-(2-thioxo-3-indoliny)butanoic acid,
4-(1-methyl-2-thioxo-3-indoliny)butanoic
acid,

methyl 4-(2-thioxo-3-indoliny)butanoate,
methyl 4-(1-methyl-2-thioxo-3-indoliny)-
butanoate,

N-phenyl (1-methyl-2-thioxo-3-indoliny)-
carboxamide,

N-phenyl (1-methyl-2-methylthio-3-indoliny)-
carboxamide,

3-benzoyl-1-methyl-2-indolinethione,
3-(4'-carboxybenzoyl)-1-methyl-
2-indolinethione,

-192-

30 3-(4'-carbomethoxybenzoyl)-1-methyl-
2-indolinethione,
and pharmaceutically acceptable salts thereof.

3. A polysulfide compound according to Claim 1
selected from

2,2'-dithiobis[methyl 2-(1-methyl-
3-indolyl)acetate],
5 bis[indolyl-3-acetic acid-(2)]trisulfide,
bis[ethyl 1-methylindolyl-3-acetate-(2)]-
disulfide,
2,2'-dithiobis[N-benzyl-2-(3-indolyl)-
acetamide],
10 bis[indolyl-3-propanoic acid-(2)]disulfide,
2,2'-dithiobis[3-(1-methyl-3-indolyl)-
propanoic acid],
bis[ethylindolyl-3-propanoate-(2)]disulfide,
2,2'-dithiobis[methyl-3-(3-indolyl)-
15 propanoate],
2,2'-dithiobis[methyl-3-(1-methyl-3-indolyl)-
propanoate],
bis[5-methylindolyl-3-propanoic acid-(2)]-
disulfide,
20 bis[ethyl-5-methylindolyl-3-propanoate-(2)]-
disulfide,
bis[6-methylindolyl-3-propanoic acid-(2)]-
disulfide,
bis[ethyl-6-methylindolyl-3-propanoate-(2)]-
25 disulfide,
bis[7-methylindolyl-3-propanoic acid-(2)]-
disulfide,
bis[ethyl-7-methylindolyl-3-propanoate-(2)]-
disulfide,

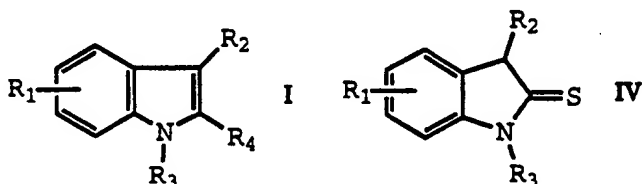
-193-

- 30 2,2'-dithiobis[N-benzyl-3-(3-indolyl)-
propanamide],
bis[indolyl-3-butanoic acid-(2)]disulfide,
2,2'-dithiobis[4-(1-methyl-3-indolyl butanoic
acid],
35 bis[methyl indolyl-3-butanoate-(2)]disulfide,
bis[methyl 1-methylindolyl-3-butanoate-(2)]-
disulfide,
bis[N-phenyl 1-methylindolyl-3-carboxamide-
(2)]disulfide,
40 bis[N-phenyl 1-ethylindolyl-3-carboxamide-
(2)]disulfide,
bis[N-phenyl 4-chloro-1-methylindolyl-
3-carboxamide-(2)]disulfide,
bis[N-phenyl 5-chloro-1-methylindolyl-
45 3-carboxamide-(2)]disulfide,
bis[N-phenyl 7-chloro-1-methylindolyl-
3-carboxamide-(2)]disulfide,
bis[N-phenyl 1-methyl-7-azaindolyl-
3-carboxamide-(2)]disulfide,
50 bis[N-phenyl 1,4-dimethylindolyl-
3-carboxamide-(2)]disulfide,
bis[N-phenyl 1,5-dimethylindolyl-
3-carboxamide-(2)]disulfide,
bis[N-phenyl 1,6-dimethylindolyl-
55 3-carboxamide-(2)]disulfide,
bis[N-phenyl 1,7-dimethylindolyl-
3-carboxamide-(2)]disulfide,
bis[N-phenyl 4-methoxy-1-methylindolyl-
3-carboxamide-(2)]disulfide,
60 bis[N-phenyl 5-methoxy-1-methylindolyl-
3-carboxamide-(2)]disulfide,
bis[N-phenyl 6-methoxy-1-methylindolyl-
3-carboxamide-(2)]disulfide,

-194-

bis[N-phenyl 7-methoxy-1-methylindolyl-
 3-carboxamide-(2)]disulfide,
 bis[N-methyl 1-methylindolyl-3-carboxamide-
 (2)]disulfide,
 bis[N-benzyl 1-methylindolyl-3-carboxamide-
 (2)]disulfide,
 bis[N-methylphenylsulfonyl]-2-indolyl]-
 disulfide,
 bis[3-benzoyl-1-methylindole-(2)]disulfide,
 bis[3-(4'-carboxybenzoyl)-1-methylindole-(2)]-
 disulfide,
 bis[3-(4'-carbomethoxybenzoyl)-
 1-methylindole(2)]disulfide,
 and pharmaceutically acceptable salts thereof.

4. A pharmaceutical composition useful for inhibition
 of protein tyrosine kinase dependent disease in a
 mammal, containing in a pharmaceutically
 acceptable carrier a therapeutically effective
 amount of a compound selected from 2-thioindole,
 2-indolinethione, and polysulfide compounds
 represented by the general Formulas I and IV



and pharmaceutically acceptable salts thereof,
 wherein

R_1 is a member selected from H, halogen, R,
 OH, OR, CF_3 , NO_2 , NH_2 , NHR , $COOH$, $CONHR$, $(CH_2)_nOH$,
 $(CH_2)_nOR$, $(CH_2)_nNH_2$, $(CH_2)_nNHR$, and $(CH_2)_nNRR$, and

-195-

further represents replacement in the ring of 1 or
2 ring methine (-CH=) atoms with aza(-N=) atoms;

R₂ is a member selected from

C₂₋₄ alkyl,

(CH₂)_nCOOH,

(CH₂)_nCOOR,

(CH₂)_nCOR,

(CH₂)_nSO₂R,

(CH₂)_nSO₂NRR,

(CH₂)_nSO₂NHR,

CH=CHCOOH,

(CH₂)_nCH-COOH,

OH

(CH₂)_nCH-COOH,

NH₂

(CH₂)_nCONH₂,

(CH₂)_nCONHR,

(CH₂)_nCONRR,

(CH₂)_nCONHCH₂Ph,

CONHR,

CONRR,

CONHPh,

COY,

COPhCOOH,

COPhCOOR,

(CH₂)_nCONHPh,

(CH₂)_nCONHPhR,

SO₂Y;

n is an integer from 1 to 4;

R is lower alkyl;

R₃ is a member selected from H, lower alkyl,
and benzyl;

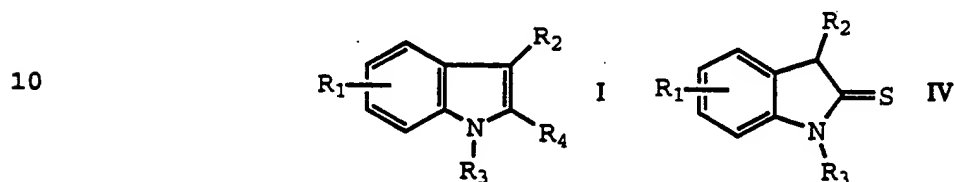
Y r presents a benzene, pyridine, thiophene,
furan, thiazole, or imidazole ring optionally

-196-

55 substituted with a lower alkyl, COOH, OH, OCOR, NH₂, CONHR, CONRR, OR, or NHR group; and

60 R₄ represents SH, S_oX, and S_oQ where o is 1, 2, or 3, X is a member selected from H, lower alkyl, benzyl, and benzene, pyridine, thiophene, furan, thiazole, and imidazole rings, and Q is another 2-thioindolyl moiety of Formula I.

5. A pharmaceutical composition useful for treating aberrant cell growth in a mammal containing in a pharmaceutically acceptable carrier a therapeutically effective amount of a compound selected from 2-thioindole, 2-indolinethione, and polysulfide compounds represented by the general Formulas I and IV



15 and pharmaceutically acceptable salts thereof, wherein

R₁ is a member selected from H, halogen, R, OH, OR, CF₃, NO₂, NH₂, NHR, COOH, CONHR, (CH₂)_nOH, (CH₂)_nOR, (CH₂)_nNH₂, (CH₂)_nNHR, and (CH₂)_nNRR, and further represents replacement in the ring of 1 or 2 ring methine (-CH=) atoms with aza(-N=) atoms;

R₂ is a member selected from

25 C₂₋₄ alkyl,
(CH₂)_nCOOH,
(CH₂)_nCOOR,
(CH₂)_nCOR,
(CH₂)_nSO₂R,

-197-

$(CH_2)_nSO_2NRR,$
 $(CH_2)_nSO_2NHR,$
 $CH=CHCOOH,$
30 $(CH_2)_nCH-COOH,$
 $\quad |$
 $\quad OH$
 $(CH_2)_nCH-COOH,$
35 $\quad |$
 $\quad NH_2$
 $(CH_2)_nCONH_2,$
 $(CH_2)_nCONHR,$
 $(CH_2)_nCONRR,$
 $(CH_2)_nCONHCH_2Ph,$
40 $CONHR,$
 $CONHPh,$
 $COY,$
 $COPhCOOH,$
 $COPhCOOR,$
45 $(CH_2)_nCONHPh,$
 $(CH_2)_nCONHPhR,$
 $SO_2Y;$

n is an integer from 1 to 4;

R is lower alkyl;

50 R_3 is a member selected from H, lower alkyl, and benzyl;

Y represents a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring optionally substituted with a lower alkyl, COOH, OH, OCOR, 55 NH_2 , CONHR, CONRR, OR, or NHR group; and

R_4 represents SH, S_oX , and S_oQ where o is 1, 2, or 3, X is a member selected from H, lower alkyl, benzyl, and benzene, pyridine, thiophene, furan, thiazole, and imidazole rings, and Q is 60 another 2-thioindolyl moiety of Formula I.

-198-

6. The compound of Claim 1 having the name
3-(2-thioxo-3-indolinyl)propanoic acid.
7. The compound of Claim 1 having the name
4-(2-thioxo-3-indolinyl)butanoic acid and
pharmaceutically acceptable salts thereof.
8. The compound of Claim 1 having the name
benzyl[N-phenyl 1-methylindolyl-3-carboxamide(2)]-
disulfide.
9. The compound of Claim 1 having the name
bis[indolyl-3-acetic acid-(2)]trisulfide.
10. The compound of Claim 1 having the name
N-benzyl(2-thioxo-3-indolinyl)acetamide and
pharmaceutically acceptable salts thereof.
11. The compound of Claim 1 having the name
bis[indolyl-3-propanoic acid-(2)]disulfide and
pharmaceutically acceptable salts thereof.
12. The compound of Claim 1 having the name
2,2'-dithiobis[3-(1-methyl-3-indolyl)propanoic
acid] and pharmaceutically acceptable salts
thereof.
13. The compound of Claim 1 having the name
bis[ethylindolyl-3-propanoate-(2)]disulfide.
14. The compound of Claim 1 having the name
2,2'-dithiobis[methyl-3-(1-methyl-3-indolyl)-
propanoate].

-199-

15. The compound of Claim 1 having the name bis[6-methylindolyl-3-propanoic acid-(2)]disulfide and pharmaceutically acceptable salts thereof.
16. The compound of Claim 1 having the name bis[ethyl-6-methylindolyl-3-propanoate(2)]-disulfide.
17. The compound of Claim 1 having the name bis[7-methylindolyl-3-propanoic acid-(2)]disulfide and pharmaceutically acceptable salts thereof.
18. The compound of Claim 1 having the name 2,2'-dithiobis[N-benzyl-3-(3-indolyl)propanamide].
19. The compound of Claim 1 having the name 2,2'-dithiobis[4-(1-methyl-3-indolyl)butanoic acid] and pharmaceutically acceptable salts thereof.
20. The compound of Claim 1 having the name bis[methyl 1-methylindolyl-3-butanate-(2)]disulfide.
21. The compound of Claim 1 having the name bis[N-phenyl 1-methylindolyl-3-carboxamide(2)]-disulfide.
22. The compound of Claim 1 having the name bis[N-phenyl 5-chloro-1-methylindolyl-3-carboxamide-(2)]disulfide.
23. The compound of Claim 1 having the name bis[N-phenyl 6-methoxy-1-methylindolyl-3-carboxamide-(2)]disulfide.

-200-

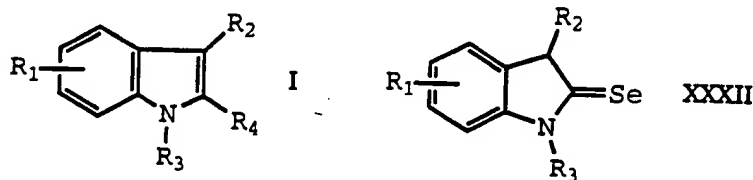
24. The compound of Claim 1 having the name bis[N-phenyl 7-methoxy-1-methylindolyl-3-carboxamide-(2)]disulfide.
25. The compound of Claim 1 having the name bis[N-methyl 1-methylindolyl-3-carboxamide(2)]-disulfide.
26. The compound of Claim 1 having the name bis[N-benzyl 1-methylindolyl-3-carboxamide(2)]-disulfide.
27. The compound of Claim 1 having the name bis[N-methylphenylsulfonyl)-2-indolyl]disulfide.
28. The compound of Claim 1 having the name bis[3-(4'-carboxybenzoyl)-1-methylindole-(2)]disulfide.
29. The compound of Claim 1 having the name bis[3-(4'-carbomethoxybenzoyl)-1-methylindole-(2)]-disulfide.
30. The compound of Claim 1 having the name methyl 3-(1-methyl-2-thioxo-3-indolinyl)propanoate.
31. The compound of Claim 1 having the name ethyl 3-(1-methyl-2-thioxo-3-indolinyl)propanoate.
32. The compound of Claim 1 having the name N-benzyl 3-(2-thioxo-3-indolinyl)propanamide.
33. A method for inhibiting protein tyrosine kinase dependent disease in a mammal, comprising

-201-

administering to said mammal a pharmaceutical composition according to Claim 4.

34. A method for treating aberrant cell growth in a mammal, comprising administering to said mammal a pharmaceutical composition according to Claim 5.
35. 2-Selenoindole, 2-indolineselenone and selenide compounds of the group represented by the general Formulas I and XXXII

5



10

and pharmaceutically acceptable salts thereof, wherein

15

R_1 is a member selected from H, halogen, R, OH, OCOR, OR, CF_3 , NO_2 , NH_2 , NHR, COOH, CONHR, $(CH_2)_nOH$, $(CH_2)_nOR$, $(CH_2)_nNH_2$, $(CH_2)_nNHR$, and $(CH_2)_nNRR$, and further represents replacement in the ring of 1 or 2 ring methine ($-CH=$) atoms with aza ($-N=$) atoms;

R_2 is a member selected from

20

C_{2-4} alkyl,
 $(CH_2)_nCOOH$,
 $(CH_2)_nCOOR$,
 $(CH_2)_nCOR$,
 $(CH_2)_nSO_2R$,
 $(CH_2)_nSO_2NRR$,
 $(CH_2)_nSO_2NHR$,
 $CH=CHCOOH$,

25

- 202 -

$$\begin{array}{l}
 (\text{CH}_2)_n \text{CH} - \text{COOH}, \\
 | \\
 \text{OH} \\
 30 \quad (\text{CH}_2)_n \text{CH} - \text{COOH}, \\
 | \\
 \text{NH}_2 \\
 (\text{CH}_2)_n \text{CONH}_2, \\
 (\text{CH}_2)_n \text{CONHR}, \\
 35 \quad (\text{CH}_2)_n \text{CONRR}, \\
 (\text{CH}_2)_n \text{CONHCH}_2\text{Ph}, \\
 \text{CONHR}, \\
 \text{CONRR}, \\
 \text{CONHPh}, \\
 40 \quad \text{COY}, \\
 \text{COPhCOOH}, \\
 \text{COPhCOOR}, \\
 (\text{CH}_2)_n \text{CONHPh}, \\
 (\text{CH}_2)_n \text{CONHPhR}, \\
 45 \quad \text{SO}_2\text{Y};
 \end{array}$$

n is an integer from 1 to 4;

R is lower alkyl;

R₃ is a member selected from H, lower alkyl, and benzyl;

50 Y represents a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring optionally substituted with a lower alkyl, COOH, OH, OCOR, NH₂, CONHR, CONRR, OR, or NHR group; and

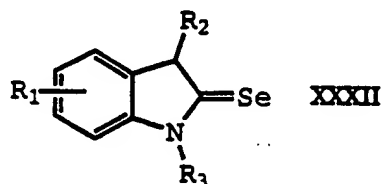
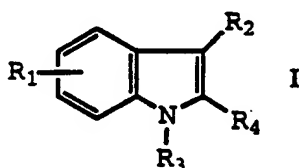
55 R_4 represents SeH , Se_oX , and Se_oQ where o is 1, 2, or 3, X is a member selected from H , lower alkyl, benzyl, and benzene, pyridine, thiophene, furan, thiazole, and imidazole rings, and Q is another 2-selenoindolyl moiety of Formula I.

36. A selenide compound according to Claim 35 selected from

-203-

2,2'-diselenobis[1-methyl-1H-indole-
 3-carboxylic acid, t-butyl ester],
 2,2'-diselenobis[1-methyl-1H-indole-
 3-carboxylic acid],
 2,2'-diselenobis[N,1-dimethyl-1H-indole-
 3-carboxamide],
 2,2'-diselenobis[N-[2-(diethylamino)ethyl]-
 1-methyl-1H-indole-3-carboxamide],
 2,2'-diselenobis[N-methyl-1H-indole-
 3-carboxamide],
 2,2'-diselenobis[N-[2-(diethylamino)ethyl]-
 1H-indole-3-carboxamide],
 2,2'-diselenobis[N-[2-(diethylamino)ethyl]-
 N-methyl-1H-indole-3-carboxamide],
 2,2'-diselenobis[1-[2-(diethylamino)ethyl]-
 N-methyl-1H-indole-3-carboxamide],
 [R-(R*,R*)]-2,2'-diselenobis[α -amino-
 N-(phenylmethyl)-1H-indole-3-propanamide], or
 [S-(R*,R*)]-2,2'-diselenobis[α -amino-
 N-(phenylmethyl)-1H-indole-3-propanamide]
 and pharmaceutically acceptable salts thereof.

37. A pharmaceutical composition useful for inhibition
 of protein tyrosine kinase dependent disease in a
 mammal, containing in a pharmaceutically
 acceptable carrier a therapeutically effective
 amount of a compound selected from 2-selenoindole,
 2-indolineselenone, and selenide compounds
 represented by the general Formulas I and XXXII



-204-

and pharmaceutically acceptable salts thereof,
wherein

15 R_1 is a member selected from H, halogen, R,
OH, OR, CF_3 , NO_2 , NH_2 , NHR, COOH, CONHR, $(CH_2)_nOH$,
 $(CH_2)_nOR$, $(CH_2)_nNH_2$, $(CH_2)_nNHR$, and $(CH_2)_nNRR$, and
further represents replacement in the ring of 1 or
2 ring methine (-CH-) atoms with aza(-N-) atoms;

20 R_2 is a member selected from

C_{2-4} alkyl,
 $(CH_2)_nCOOH$,
 $(CH_2)_nCOOR$,
 $(CH_2)_nCOR$,
25 $(CH_2)_nSO_2R$,
 $(CH_2)_nSO_2NRR$,
 $(CH_2)_nSO_2NHR$,
CH=CHCOOH,
30 $(CH_2)_nCH-COOH$,
|
OH
 $(CH_2)_nCH-COOH$,
|
NH₂
35 $(CH_2)_nCONH_2$,
 $(CH_2)_nCONHR$,
 $(CH_2)_nCONRR$,
 $(CH_2)_nCONHCH_2Ph$,
CONHR,
40 CONRR,
CONHPh,
COY,
COPhCOOH,
COPhCOOR,
45 $(CH_2)_nCONHPh$,
 $(CH_2)_nCONHPhR$,
SO₂Y;

n is an integer from 1 to 4;

-205-

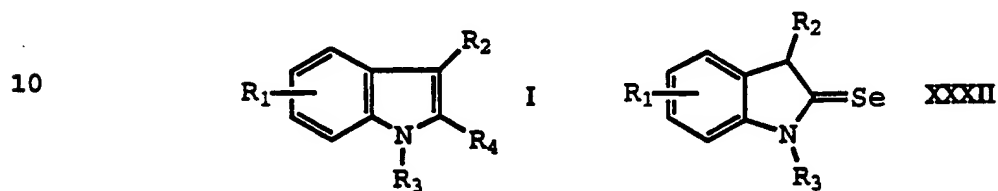
R is lower alkyl;

50 R₃ is a member selected from H, lower alkyl, and benzyl;

Y represents a benzene, pyridine, thiophene, furan, thiazole, or imidazole ring optionally substituted with a lower alkyl, COOH, OH, OCOR, 55 NH₂, CONHR, CONRR, OR, or NHR group; and

R₄ represents SeH, Se_oX, and Se_oQ where o is 1, 2, or 3, X is a member selected from H, lower alkyl, benzyl, and benzene, pyridine, thiophene, furan, thiazole, and imidazole rings, and Q is 60 another 2-selenoindolyl moiety of Formula I.

38. A pharmaceutical composition useful for treating aberrant cell growth in a mammal containing in a pharmaceutically acceptable carrier a therapeutically effective amount of a compound 5 selected from 2-selenoindole, 2-indolineselenone, and selenide compounds represented by the general Formulas I and XXXII



15 and pharmaceutically acceptable salts thereof, wherein

R₁ is a member selected from H, halogen, R, OH, OR, CF₃, NO₂, NH₂, NHR, COOH, CONHR, (CH₂)_nOH, (CH₂)_nOR, (CH₂)_nNH₂, (CH₂)_nNHR, and (CH₂)_nNRR, and further represents replacement in the ring of 1 or 20 2 ring methine (-CH=) atoms with aza(-N=) atoms;

R₂ is a member selected from

-206-

C₂₋₄ alkyl,
 (CH₂)_nCOOH,
 (CH₂)_nCOOR,
 25 (CH₂)_nCOR,
 (CH₂)_nSO₂R,
 (CH₂)_nSO₂NRR,
 (CH₂)_nSO₂NHR,
 CH=CHCOOH,
 30 (CH₂)_nCH-COOH,
 |
 OH
 (CH₂)_nCH-COOH,
 35 |
 NH₂
 (CH₂)_nCONH₂,
 (CH₂)_nCONHR,
 (CH₂)_nCONRR,
 (CH₂)_nCONHCH₂Ph,
 40 CONHR,
 CONHPh,
 COY,
 CPhCOOH,
 CPhCOOR,
 45 (CH₂)_nCONHPh,
 (CH₂)_nCONHPhR,
 SO₂Y;

n is an integer from 1 to 4;

R is lower alkyl;

50 R₃ is a member selected from H, lower alkyl,
and benzyl;

Y represents a benzene, pyridine, thiophene,
furan, thiazole, or imidazole ring optionally
substituted with a lower alkyl, COOH, OH, OCOR,
55 NH₂, CONHR, CONRR, OR, or NHR group; and

R₄ represents SeH, Se_oX, and Se Q where o is
1, 2, or 3, X is a member selected from H, lower

-207-

alkyl, benzyl, and benzene, pyridine, thiophene, furan, thiazole, and imidazole rings, and Q is another 2-selenoindolyl moiety of Formula I.

60

39. The compound of Claim 35 having the name [R-(R*,R*)]-2,2'-diselenobis[α -amino-N-(phenylmethyl)-1H-indole-3-propanamide].
40. The compound of Claim 35 having the name [S-(R*,R*)]-2,2'-diselenobis[α -amino-N-(phenylmethyl)-1H-indole-3-propanamide].
41. The compound of Claim 35 having the name 2,2'-diselenobis[1-methyl-1H-indole-3-carboxylic acid, t-butyl ester].
42. The compound of Claim 35 having the name 2,2'-diselenobis[1-methyl-1H-indole-3-carboxylic acid].
43. The compound of Claim 35 having the name 2,2'-diselenobis[N,1-dimethyl-1H-indole-3-carboxamide].
44. The compound of Claim 35 having the name 2,2'-diselenobis[N-[2-(diethylamino)ethyl]-1-methyl-1H-indole-3-carboxamide].
45. The compound of Claim 35 having the name 2,2'-diselenobis[N-1-methyl-1H-indole-3-carboxamide].

-208-

46. The compound of Claim 35 having the name
2,2'-diselenobis[N-[2-(diethylamino)ethyl]-
1H-indole-3-carboxamide].
47. The compound of Claim 35 having the name
2,2'-diselenobis[N-[2-(diethylamino)ethyl]-
N-methyl-1H-indole-3-carboxamide].
48. The compound of Claim 35 having the name
2,2'-diselenobis[1-[2-(diethylamino)ethyl]-
N-methyl-1H-indole-3-carboxamide].
49. A method for inhibiting protein tyrosine kinase
dependent disease in a mammal comprising
administering to said mammal a pharmaceutical
composition according to Claim 37.
50. A method for treating aberrant cell growth in a
mammal, comprising administering to said mammal a
pharmaceutical composition according to Claim 38.

INTERNATIONAL SEARCH REPORT

PCT/US 93/07272

International Application No. _____

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5	C07D209/30; C07D401/14;	C07D209/42; C07D471/04;
	C07D405/14; A61K31/40;	C07D409/14 A61K31/44
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D ; A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE vol. 1, 1987, pages 181 - 188 'A new preparation of N-aryl-1-alkynesulphenamides and their thermal rearrangements into indoline-2-thiones' *see compounds of examples 29,30 and 32* ---	1
X	TETRAHEDRON vol. 42, 1986, pages 5879 - 5886 'Synthesis of debromo-8,8a-dihydroflustramine C, a model synthesis towards amauromine' cited in the application *see compound number 12, page 5881* --- -/--	1
<p>⁹ Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
29 NOVEMBER 1993	- 9. 12. 93	
International Searching Authority	Signature of Authorized Officer	
EUR PEAN PATENT OFFICE	SCRUTON-EVANS I.	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claims No.
A	TETRAHEDRON LETTERS vol. 31, 1990, pages 7229 - 7232 'Selectivity in the Thiocyanation of 3-alkylindoles: An unexpectedly easy access to 2-isothiocyano derivatives' cited in the application ---	1-32
T	JOURNAL OF MEDICINAL CHEMISTRY vol. 36, 1993, pages 2459 - 2469 'Tyrosine kinase inhibitors' ---	1-32, 35-48
A	WO,A,9 113 055 (FARMITALIA CARLO ERBA S.R.L) 5 September 1991 ---	1-32, 35-48
P,A	US,A,5 196 446 (YISSUM RESEARCH DEVELOPMENT CO. OF THE HEBREW UNIVERSITY OF JERUSALEM) 23 March 1993 -----	1-32

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9307272
SA 78016

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 29/11/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9113055	05-09-91	AU-A- 7241291	18-09-91
		EP-A- 0470221	12-02-92
		JP-T- 4506081	22-10-92

US-A-5196446	23-03-93	AU-A- 7756891	11-11-91
		EP-A- 0527181	17-02-93
		WO-A- 9116305	31-10-91

EPO FORM P0079

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82